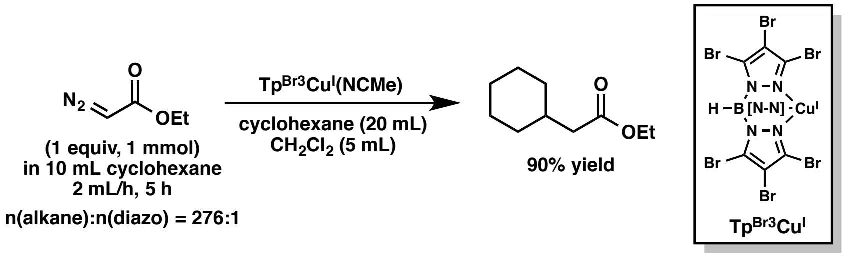
APPENDIX 7

Copper-Catalyzed Insertion of Carbenoids into Unactivated C(sp^3)–H Bonds

A7.1 Introduction

Direct functionalization of C–H bonds is a much desired goal in chemistry due to the ubiquity of C–H bonds and the potential to streamline the synthetic sequence.[1] However, C–H bonds are unreactive and often require transition metal complexes for activation and subsequent transformations.[2] Metal carbenoid insertion into C–H bonds, which forms a new C–C bond, is a viable approach and has witnessed rapid growth in the past few decades.[3] The vast majority of examples rely on rhodium, a rare and expensive metal, as catalyst.[4] From an economic perspective, it is more desirable to use earth-abundant first row transition metal catalysts. This area is much less developed. So far, the only successful system is based on copper-tris(pyrazolyl)borate complexes that catalyze the dediazotization of ethyl diazoacetate and insertion of the resulting copper carbenoid into unactivated C(sp^3)–H bonds of alkanes such as cyclohexane (Scheme A7.1).[5]

Scheme A7.1 Copper-tris(pyrazolyl)borate-catalyzed carbenoid C–H insertions



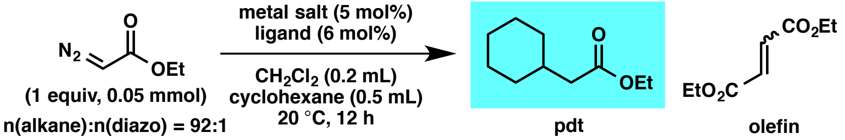
As a member of the NSF Center for Selective C–H Functionalization, our group became interested in developing new C–H functionalization chemistry using earth-abundant transition metals or main group metals. Although the aforementioned copper system partially addresses this challenge, it requires an exotic ligand and a huge excess of either the alkane substrate or the diazo reagent. We envisioned that a combinatorial screen of metals, ligands, and additives might allow us to spot a readily available catalyst system that performs the task more efficiently. We also wanted to explore C–H functionalization in a complex molecular setting and test the chemo-, regio-, and stereoselectivity of our new catalytic system.

A7.2 Results and Discussions

At the outset of our investigation, we chose cyclohexane as the model alkane substrate and ethyl diazoacetate as the carbenoid precursor. The alkane was used in excess (92:1 molar ratio of alkane to diazo), but not as much as in the literature (276:1, see Scheme A7.1). The desired product (ethyl cyclohexyl-acetate) and olefin side products (diethyl maleate/diethyl fumarate, resulting from carbenoid dimerization) are all commercially available. Thus, a simple GC assay enables quantitative measurement of yield and selectivity. Selectivity is defined as the ratio of desired product peak area to the total peak areas of both the desired product and olefin side products.

First, we surveyed a combination of first-row transition metal triflates and ligands for their ability to catalyze the carbenoid insertion reaction (Table A7.1). Manganese(II), iron(II), and nickel(II) triflates were all ineffective at dediazotization since neither the desired insertion product nor olefin byproducts were observed. Copper(II) triflate, on the other hand, catalyzed dediazotization efficiently. Unfortunately, the desired insertion product was formed in only trace amounts, while the vast majority of the diazo reagent went into the olefin side products.

Table A7.1 Screen of metal salts and ligands [a]

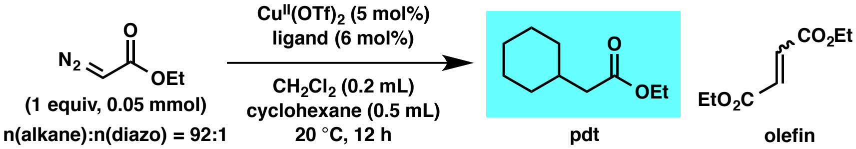


metal / ligand	$Mn^{II}(OTf)_2$	$Fe^{II}(OTf)_2$	$Ni^{II}(OTf)_2$	$Cu^{II}(OTf)_2$	% selectivity[b] [for $Cu^{II}(OTf)_2$]
2,2'-bipy	0	0	0	0.9	4
1,10-phen	0	0	0	2.2	9
(*S*)-*t*-BuPHOX	0	0	0	1.2	4
PPh_3	0	0	0	1.4	7
PCy_3	0	0	0	1.9	7

[a] Yield of desired insertion product determined by GC using tridecane as internal standard.
[b] Selectivity = A(pdt)/[A(pdt)+A(olefin)].

Having identified Cu(OTf)$_2$ as a uniquely effective metal catalyst, we proceeded to investigate the effect of ligands (Table A7.2). Phosphine ligands (except bis(dicyclohexylphosphino)butane, entry 5) did not improve product yield but increased selectivity (entries 1–4, 6–8). In the absence of ligand, the reaction proceeded with slightly higher yield (entry 9).

Table A7.2 Screen of ligands with Cu(OTf)$_2$ [a]

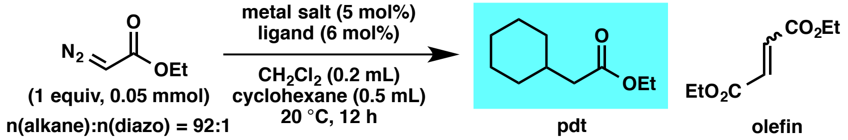


entry	ligand	% pdt yield	% selectivity^b
1	dppm	2.3	12
2	dppe	2.7	16
3	dppp	1.9	8
4	dppb	2.3	13
5	dcypb	0	
6	dppf	2.2	13
7	(2-biph)P(*t*-Bu)$_2$	2.0	17
8	Xantphos	2.2	12
9		3.9	15

[a] Yield of desired insertion product determined by GC using tridecane as internal standard. [b] Selectivity = A(pdt)/[A(pdt)+A(olefin)].

Next, we investigated other metal salts (copper and non-copper) with or without ligand (Table A7.3). We found that (MeCN)$_4$Cu^{I}PF$_6$ was a more effective catalyst in both yield and selectivity than any salt/ligand combination previously screened (entry 3). Lewis acidic main group metal salts, which are expected to be able to dediazotize ethyl diazoacetate, proved to be ineffective (entries 5 and 6).

Table A7.3 Screen of other metal salts [a]



entry	metal salt	ligand	% pdt yield	% selectivity[b]
1	$Cu^{II}Cl_2$	1,10-phen	0	
2	$Cu^{II}(O\textit{i}\text{-}Bu)_2$	1,10-phen	0	
3	$(MeCN)_4Cu^{I}PF_6$		7.8	37
4	$(\textit{R,R})\text{-}Co^{II}(\textit{t}\text{-}Bu_4Salen)$		0	
5	$Ca^{II}(O\textit{i}\text{-}Pr)_2$		0	
6	$Mg^{II}Br_2{\bullet}OEt_2$		0	
7	$Co^{II}Cl_2$	1,10-phen	0	
8	$Co^{II}Br_2$	1,10-phen	0	
9	$Cr^{II}Cl_2$	1,10-phen	0	

[a] Yield of desired insertion product determined by GC using tridecane as internal standard. [b] Selectivity = A(pdt)/[A(pdt)+A(olefin)].

Since Cu^{I} was found to be more effective than Cu^{II} salts, we next performed a screen of additives/ligands with $(MeCN)_4Cu^{I}PF_6$ (Figure A7.1) as well as with $Cu^{I}(OTf)$•toluene (Figure A7.2). The best results are summarized in Table A7.4. Generally, we found that additives bearing acidic protons promote the desired C–H insertion. In particular, carbanilide (entry 1) gave the highest selectivity for the desired insertion product (51%). However, the highest yield is only 11.6%, not much higher than that of the ligand-free conditions (8.7%, entry 6; see also Table A7.3, entry 3). These results demonstrate that the acidic additives could inhibit carbenoid dimerization, which forms the olefin side products, but could not significantly promote C–H insertion.

Figure A7.1 Additives/ligands with $(MeCN)_4Cu^IPF_6$

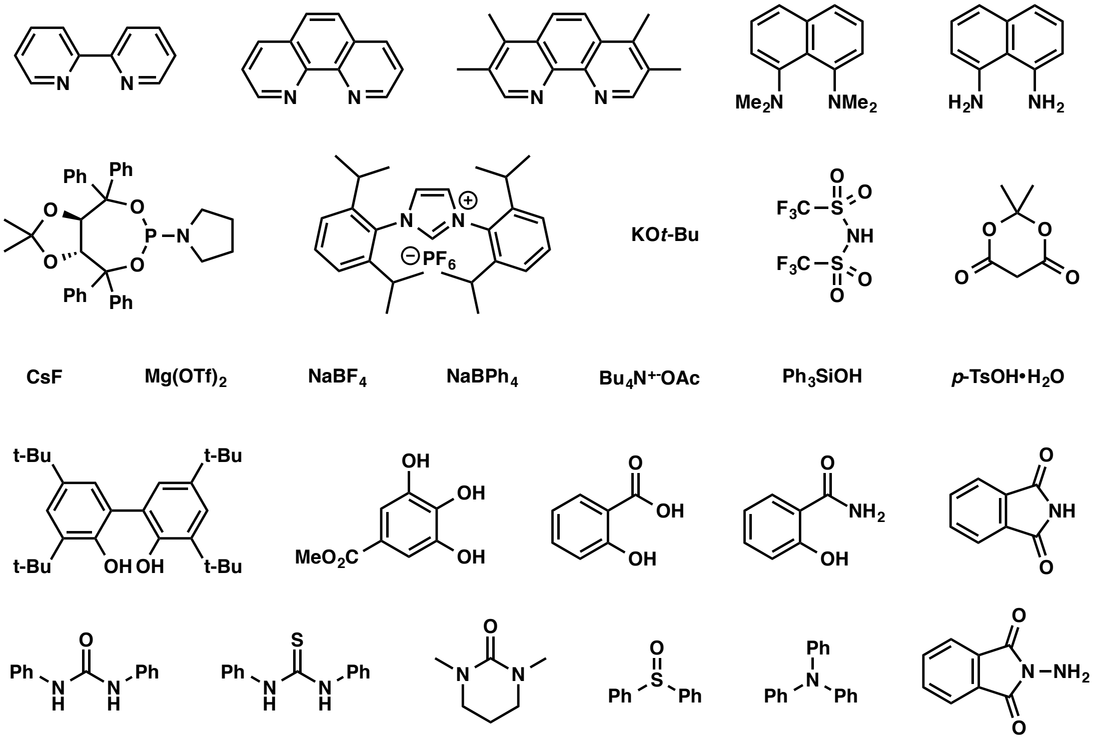


Figure A7.2 Additives/ligands with $Cu^I(OTf)$*•toluene*

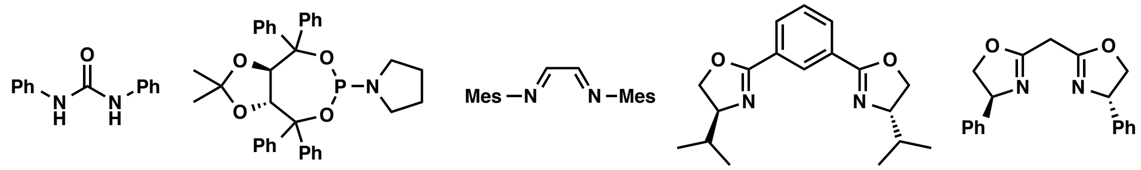
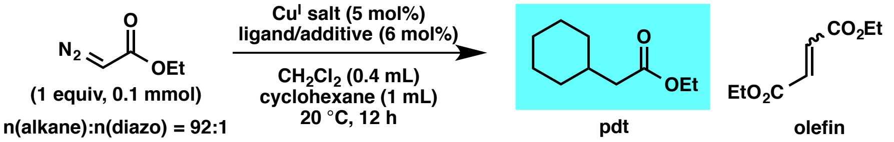
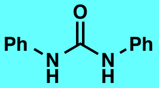
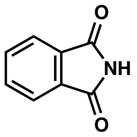
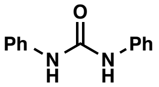
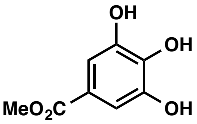


Table A7.4 Top results from the additive/ligand screen with Cu^I sources

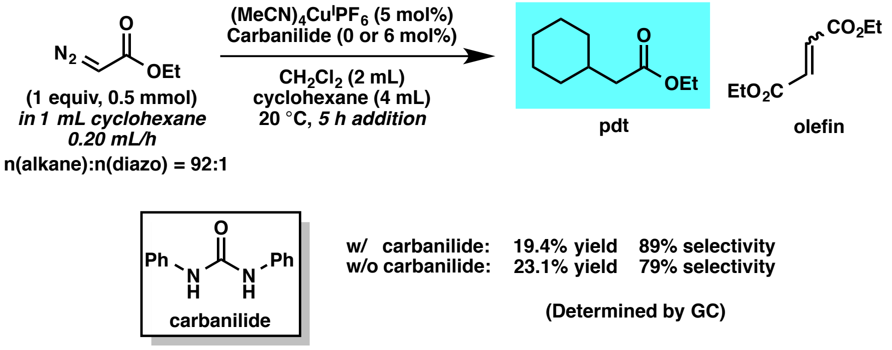


entry	Cu^I salt	ligand/additive	% pdt yield[a]	% selectivity[b]
1	$(MeCN)_4Cu^IPF_6$		11.6	51
2	$(MeCN)_4Cu^IPF_6$	Tf_2NH	11.6	47
3	$(MeCN)_4Cu^IPF_6$		10.5	50
4	Cu^I(OTf)•toluene		10.0	41
5	$(MeCN)_4Cu^IPF_6$		9.8	38
6	$(MeCN)_4Cu^IPF_6$	none	8.7	39

[a] Yield of desired insertion product determined by GC using tridecane as internal standard. [b] Selectivity = A(pdt)/[A(pdt)+A(olefin)].

In all the screening reactions described above, the diazo reagent was added to the reaction mixture in one shot. Previous literature has suggested that slow addition of diazo reagent could minimize carbenoid dimerization. To test that hypothesis in our system, we performed slow-addition experiments using the optimal conditions identified so far (Scheme A7.2). We were delighted to observe that the yield indeed increased to ~20%, and selectivity rose to ~80%. Addition of carbanilide improved selectivity but decreased yield slightly.

Scheme A7.2 Slow-addition experiments

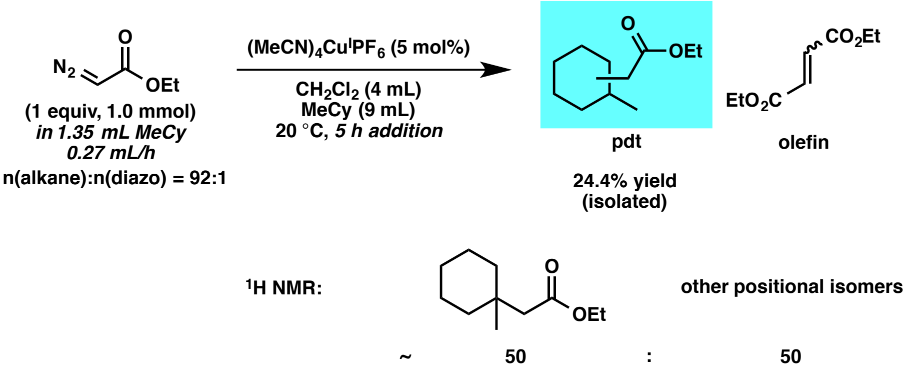


w/ carbanilide: 19.4% yield 89% selectivity
w/o carbanilide: 23.1% yield 79% selectivity

(Determined by GC)

In addition to cyclohexane, we also explored methylcyclohexane as substrate because it contains all three types of alkyl C–H bonds (primary, secondary, and tertiary) and allows us to test the system's chemoselectivity (Scheme A7.3). The insertion products were isolated in 24.4% yield. ^{1}H NMR analysis indicated the product to be a mixture of positional isomers, half of which is the tertiary C–H insertion product.

Scheme A7.3 Methylcyclohexane as substrate



A7.3 Concluding Remarks

We have investigated first-row transition metal-catalyzed carbenoid C–H insertion into simple alkanes. Extensive screen of metal salts, ligands, and additives led to the identification of $(MeCN)_4Cu^IPF_6$ as a uniquely effective catalyst. Additives such as carbanilide are capable of suppressing carbenoid dimerization but not improving product yield. While reactions using simple alkane substrates certainly need further improvement, we believe that future studies should focus on selective C–H functionalization of more complex substrates such as terpenes and steroids.

A7.4 Experimental Section

A7.4.1 Materials and Methods

All reactions were performed in flame-dried glassware under a nitrogen atmosphere using dry, deoxygenated solvents. Cyclohexane was distilled over CaH_2 under N_2 and transferred into the glove box. Ethyl diazoacetate was purchased from Sigma-Aldrich and used as received. Yield was determined using an Agilent 6850 GC (HP-1 column) with tridecane as internal standard.

A7.4.2 Procedure for Screening Reactions

In a nitrogen-filled glovebox, a 1-dram vial equipped with a magnetic stir bar was charged with ligand (0.003 mmol, 0.06 equiv) and metal salt (0.0025 mmol, 0.05 equiv). CH_2Cl_2 (0.2 mL) was added, and the mixture was stirred for 10 min. A stock solution of ethyl diazoacetate in cyclohexane (13.4 mg/mL, 0.5 mL, 0.05 mmol, 1.0 equiv) was added in one shot to the vial, which was then sealed with a PTFE screw cap. The reaction mixture was stirred at 20 °C for 10 h, and tridecane (12 μL, 0.05 mmol, 1.0 equiv) was added. The mixture was filtered through a small plug of silica (eluting with CH_2Cl_2), and the eluent was analyzed by GC.

A7.4.3 Procedure for Preparative Scale Reactions

In a nitrogen-filled glove box, a 25 mL round-bottom flask equipped with a magnetic stir bar was charged with $(MeCN)_4Cu^IPF_6$ (9.3 mg, 0.025 mmol, 0.05 equiv), CH_2Cl_2 (2 mL), and cyclohexane (4 mL). The flask was sealed with a rubber septum, brought out of the glove box, and connected to a N_2 manifold. A solution of ethyl diazoacetate (67 mg, 0.5 mmol, 1.0 equiv) in cyclohexane (1 mL) was added slowly over 5 h using a syringe pump. After addition was complete, the reaction mixture was either analyzed by GC or concentrated and subjected to silica gel flash column chromatography (2% Et_2O in hexanes) to isolate the insertion product.

A7.5 Notes and References

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(2) (a) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514.

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(4) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424.

(5) (a) Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896–897. (b) Caballero, A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 1446–1447.