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Cu/PCy$_3$-catalyzed formal carbene insertion into electron-deficient C–H bonds

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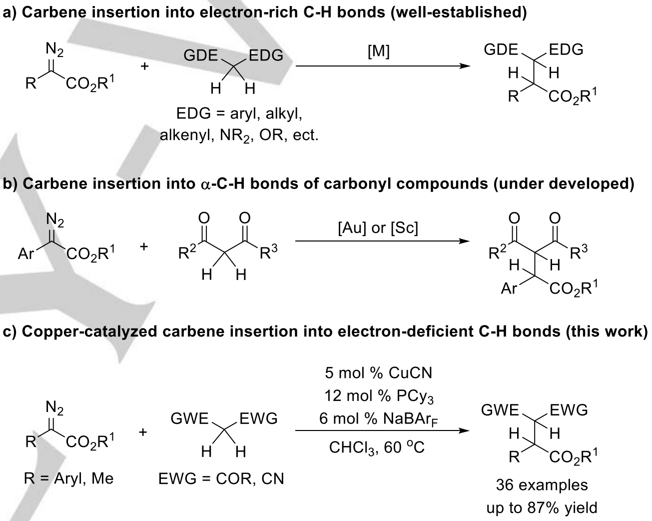
Abstract: A carbene insertion into electron-deficient C–H bonds of 1,3-diesters, β-ketoesters, β-ketonitriles, and malononitriles was realized by using CuCN/PCy$_3$ as a catalyst. The reaction provides a straightforward approach to the synthetically important multi-substituted succinic acid derivatives. A plausible reaction mechanism with cyclopropanation/ring opening as key steps was proposed based on control experiments.

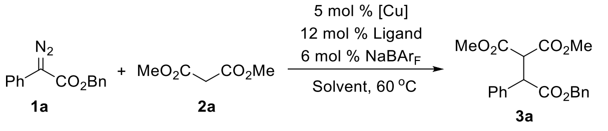
As an efficient method for the C–H bond functionalization, transition-metal-catalysed carbene insertion into C–H bonds achieved a great progress and has been widely used in organic synthesis.[1] The activity and selectivity of C–H bond insertion reactions are affected by both the steric and electronic properties of the C–H bonds. In general, the C–H bonds with α-electron-donating groups have higher electron density and higher reactivity in the insertion reactions (Scheme 1a). On the contrary, the C–H bonds with α-electron-withdrawing groups have lower electron density and lower reactivity in the insertion reactions. So far, only a few carbene insertion reactions of electron-deficient C–H bonds with α-carbonyl groups have been reported (Scheme 1b),[2] although such reactions are potentially useful for the preparation of multifunctional molecules. The intramolecular carbene insertion into the C–H bonds with α-carbonyl groups was achieved by using rhodium catalysts,[2a-2c] but only very special substrates with cage structure have high yields.[2c] The intermolecular carbene insertion into the electron-deficient C–H bonds is more challenging, and the chemoselectivity of reaction using copper or dirhodium catalysts is poor.[2d,e] Quite recently, several gold catalysts,[2f,g] copper catalysts,[2h] scandium catalysts,[2i] diene-Rh(I) catalysts[2j] were developed for the intermolecular carbene insertion into the C–H bonds of 1,3-diketones, cyclic lactones and β-ketoesters. The known catalysts for carbene insertion into electron-deficient C–H bonds are highly substrate dependent. For instance, the carbene insertion into the α-C–H bonds of nitriles still lacks efficient catalysts. As a part of our long-lasting interest in catalytic carbene insertion reactions,[3] we herein report an electron-deficient formal C–H bond insertion reaction catalyzed by copper catalysts modified with monodentate phosphine ligands (Scheme 1c). With this protocol, various electron-deficient α- C–H bonds of 1,3-diesters, β-ketoesters, β-ketonitriles, and malononitriles could undergo the carbene insertion reaction to generate multi-functionalized products with good to high yields.



Scheme 1. Transition-metal-catalysed carbene insertion into C–H bonds

Our study began with the reaction of benzyl α-diazo-α-phenylacetate (**1a**) and methyl malonate (**2a**) performed at 60 °C in CHCl$_3$. Copper salts (including CuCl, CuPF$_6$(MeCN)$_4$, CuOTf.1/2toluene, CuSO$_4$, CuCl$_2$) or their complexes with phosphine ligands can decompose diazoester **1a**, but gave complicated mixture without the desired product (data not shown). To our delight, when NaBAr$_F$ (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) was added, the reactions promoted by CuCN/PBu$_3$ completed in 20 h, resulting in the desired formal C–H bond insertion product **3a** with a yield of 61% (Table 1, entry 1). The bulky and non-coordinative BAr$_F^-$ protected the active copper(I) catalyst species and increased their Lewis acidity in the reaction.[4]

Table 1. Copper-catalyzed formal carbene insertion into C–H bond of **2a**: optimization of reaction conditions [a]

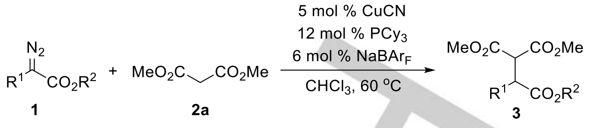


Entry	[Cu]	Ligand	Solvent	t (h)	Yield (%)[b]
1	CuCN	PBu_3	$CHCl_3$	20	61
2	CuCN	PCy_3	$CHCl_3$	1	85
3	CuCN	PPh_3	$CHCl_3$	1	49
4	CuCN	$P(OMe)_3$	$CHCl_3$	0.5	11
5[c]	CuCN	dppe	$CHCl_3$	1	19
6[d]	CuCN	dppb	$CHCl_3$	1	49
7[e]	CuCN	dppf	$CHCl_3$	1.5	51
8[f]	CuCN	TMEDA	$CHCl_3$	1	24
9	CuCl	PCy_3	$CHCl_3$	1	26
10	CuI	PCy_3	$CHCl_3$	24	40
11[g]	CuTc	PCy_3	$CHCl_3$	1	47
12	CuCN	PCy_3	DCE	1	79
13	CuCN	PCy_3	MeCN	2	73
14	CuCN	PCy_3	toluene	2	73
15	CuCN	PCy_3	THF	2	72

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), [Cu] (0.02 mmol, 5 mol%), ligand (0.048 mmol, 12 mol%), $NaBAr_F$ (6 mol%), $CHCl_3$ (4 mL), 60 °C. [b] Isolated yield based on **1a**. [c] dppe = 1,2-bis(diphenylphosphino)ethane. [d] dppb = 1,4-bis(diphenylphosphino)butane. [e] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [f] TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. [g] CuTc = copper(I) thiophene-2-carboxylate.

The effect of ligands was then studied (entries 2–8). Although monodentate and bidentate phosphine ligands as well as the diamine ligand TMEDA all can promote the formal C–H bond insertion reaction, the electron-rich and sterically hindered tricyclohexylphosphane (PCy_3) exhibited the highest yield (85%, entry 2). In the presence of ligand PCy_3, the precursors of copper catalysts were compared and the CuCN was found to be the best choice (entries 2 and 9–11). Besides $CHCl_3$, DCE, CH_3CN, toluene, and THF were also suitable solvents for the reaction (entries 12–15).

Table 2. Copper-catalyzed formal carbene insertion into C–H bond of **2a** using different α-diazoesters.[a]

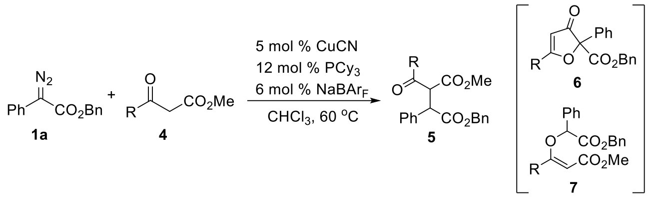


Entry	R^1	R^2	**1**	t (h)	**3**	Yield (%)[b]
1	Ph	Bn	**1a**	1.5	**3a**	85
2	Ph	Me	**1b**	1	**3b**	65
3	Ph	^{t}Bu	**1c**	1	**3c**	31
4	2-$MeOC_6H_4$	Bn	**1d**	0.5	**3d**	80
5	3-$MeOC_6H_4$	Bn	**1e**	5	**3e**	78
6	4-$MeOC_6H_4$	Bn	**1f**	0.5	**3f**	85
7	3-MeC_6H_4	Bn	**1g**	1.5	**3g**	78
8	4-MeC_6H_4	Bn	**1h**	0.5	**3h**	81
9	3,4-$(MeO)_2C_6H_4$	Bn	**1i**	0.5	**3i**	87
10	2-ClC_6H_4	Bn	**1j**	1	**3j**	74
11	3-ClC_6H_4	Bn	**1k**	2	**3k**	78
12	4-ClC_6H_4	Bn	**1l**	5	**3l**	77
13	4-BrC_6H_4	Bn	**1m**	2	**3m**	75
14	2-naphth	Bn	**1n**	1.5	**3n**	82
15	3-thienyl	Bn	**1o**	2	**3o**	26
16	Me	Bn	**1p**	5	**3p**	11
17	H	Bn	**1q**	2	**3q**	trace

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol), 5 mol% CuCN, 12 mol% PCy_3, 6 mol% $NaBAr_F$, $CHCl_3$ (4 mL), 60 °C. [b] Isolated yield based on **1**.

Having established the reaction conditions, we tested a variety of α-diazoesters to probe the versatility of this catalytic system (Table 2). Changing the ester group (R^2) of diazoester from Bn to small methyl and bulky *tert*-butyl resulted in lower yield (entries 2 and 3). The steric and electronic properties of the substituents on the benzene ring of diazoesters **1** slightly affected the yield of reaction (entries 4–14). Furthermore, α-diazo-α-(thiophen-3-yl)acetate (**1o**) and α-diazopropanoate (**1p**) can also undergo the reaction, albeit at low yields (26% and 11%, respectively) (entries 15 and 16). However, only a trace amount of the desired product was obtained when the α-diazoacetate (**1q**) was used as substrate (entry 17).

Table 3. Copper-catalyzed carbene insertion into C–H bonds of β-ketoesters.[a]

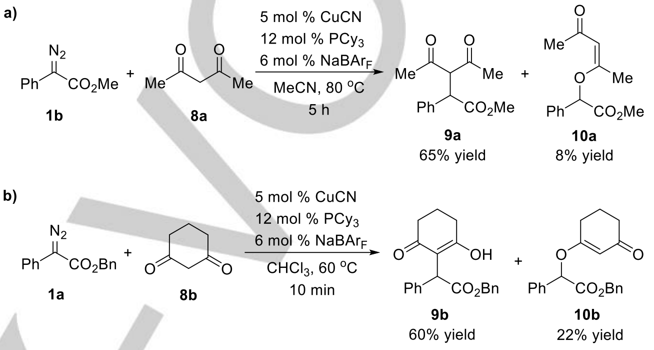


Entry	R	t (h)	dr	Yield (%)[b]		
				5	**6**	**7**
1	Ph	0.5	78:22	79 (**5a**)	9	--[d]
2	4-MeOC$_6$H$_4$	1	77:23	79 (**5b**)	6	--
3	4-MeC$_6$H$_4$	1	73:27	78 (**5c**)	4	--
4	4-ClC$_6$H$_4$	0.5	77:23	80 (**5d**)	11	--
5	4-CF$_3$C$_6$H$_4$	0.5	76:24	75 (**5e**)	11	5
6	2-ClC$_6$H$_4$	0.5	63:37	47 (**5f**)	12	27
7	2-MeC$_6$H$_4$	0.5	63:37	66 (**5g**)	3	11
8	2-naphthyl	0.5	73:27	83 (**5h**)	8	--
9	2-furyl	1	67:33	76 (**5i**)	--	--
10	Me	0.5	61:39	74 (**5j**)	--	10
11	^{n}Pr	1	66:34	70 (**5k**)	--	8
12	^{i}Pr	0.5	76:24	57 (**5l**)	--	7
13	^{t}Bu	1.5	62:38	54 (**5m**)	--	8

[a] Reaction conditions: **1a** (0.4 mmol), **4** (0.8 mmol), 5 mol% CuCN, 12 mol% PCy$_3$, 6 mol% NaBAr$_F$, CHCl$_3$ (4 mL), 60 °C. [b] Isolated yield based on **1a**.

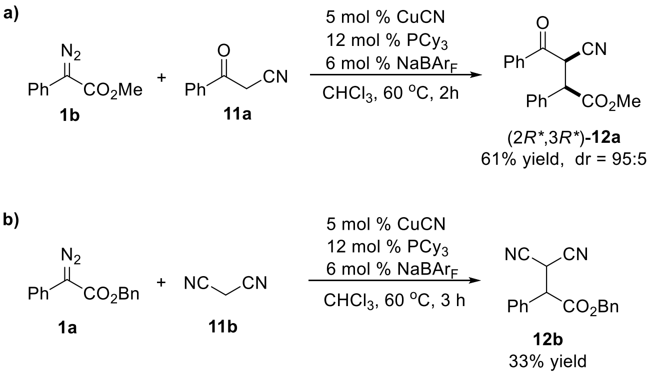
We next evaluated the reactivity of other electron-deficient C–H bonds. To our delight, the catalyst Cu/PCy$_3$ was applicable to β-aryl-, or β-alkyl-β-ketoesters, providing the desired C–H bond insertion products with moderate to good yields. While the diastereoselectivities of reaction were 61:39 to 78:22 (Table 3). Introduction of electron-donating or electron-withdrawing groups at 4-position of aryl ring of β-aryl-β-ketoesters had little effect on the yield and diastereoselectivity of reaction (entries 1–5). However, 2-substituent, especially 2-Cl, on the aryl ring of β-aryl-β-ketoesters lead to a decrease of yield (47% and 66%, respectively, entries 6 and 7). The β-ketoesters with 2-naphthyl or 2-furyl also worked well, giving the corresponding products with good yields (entries 8 and 9). As for β-alkyl-β-ketoesters substrates, the steric hindrance has a negative influence on the yield of reaction (entries 10–13). Two major by-products **6** and **7** were detected in the reactions with substrates **4**. The structure of (2*R**,3*S**)-**5e** (major isomer) was confirmed by analysis of single-crystal X-ray defraction.[5]

We next explored the carbene insertion into C–H bonds of 1,3-diketones (Scheme 2). Acetylacetone reacted with diazo **1b** to give 65% of C–H bond insertion product **9a** and 8% of enol O–H insertion product **10a**. Similarly, 1,3-cyclohexanedione provided 60% of C–H bond insertion product **9b**, which exists in enol form, and 22% of the enol O–H insertion product **10b**.



Scheme 2. C–H bond insertion with 1,3-diketones.

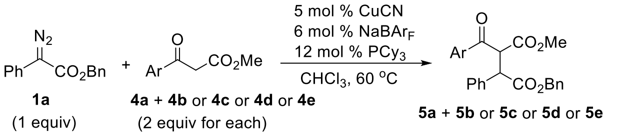
Noteworthy, the copper-catalyzed carbene insertion reaction can be extended to the α-C–H bond of nitrile compounds **11a** and **11b** to generate the desired products **12a** and **12b** in 61% and 33% yield, respectively (Scheme 3). Excellent diastereoselectivity (95:5 dr) was observed in the insertion product **12a**. The structure of (2*R**,3*R**)-**12a** (the major isomer) was confirmed by analysis of single-crystal X-ray diffraction.[5] The yield of the reaction of malononitrile is lower than that of β-carbonyl nitrile, which may be attributed to its slow enolization.



Scheme 3. C–H bond insertion reactions with nitriles.

To understand the reaction mechanism, we studied the relationship between the degree of enolization of β-ketoesters and their reactivity in the carbene insertion reaction. The relative reaction rates of β-ketoester **4a** and *para*-substituted β-ketoesters **4b**–**4e** were measured by competitive experiments. The data in Table 4 indicated that the reactivity of β-ketoester increases with the degree of enolization, and showed a good linear relationship (Figure 1).

Table 4. Relative C–H bond insertion reactivity of different *β*-ketoesters.



Ar	4-OMeC$_6$H$_4$	4-MeC$_6$H$_4$	Ph	4-ClC$_6$H$_4$	4-CF$_3$C$_6$H$_4$
Enol (%)[a]	7.4	10.7	16.7	24.8	35.9
Relative rate to **4a**[b]	0.35	0.56	1.00	1.82	2.79

[a] Determined by ^{1}H NMR. [b] The ratio of C–H bond insertion product of *para*-substituted β-ketoester to **4a**.

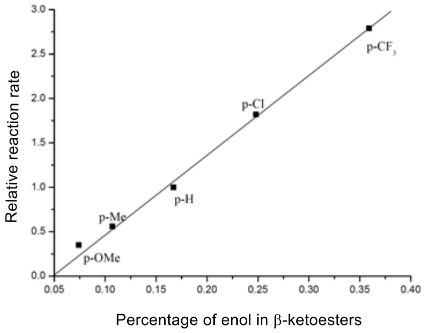
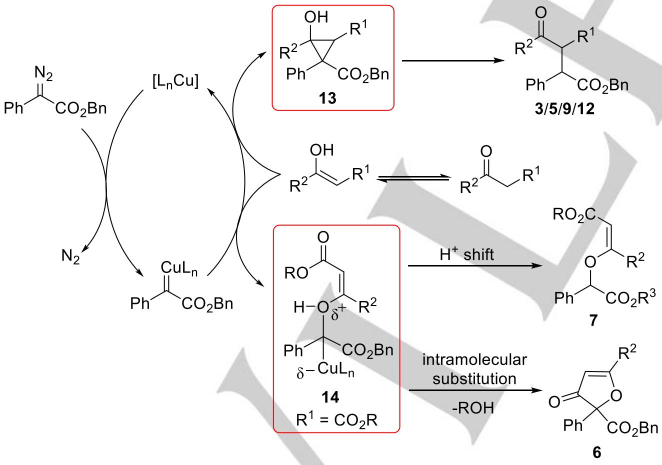


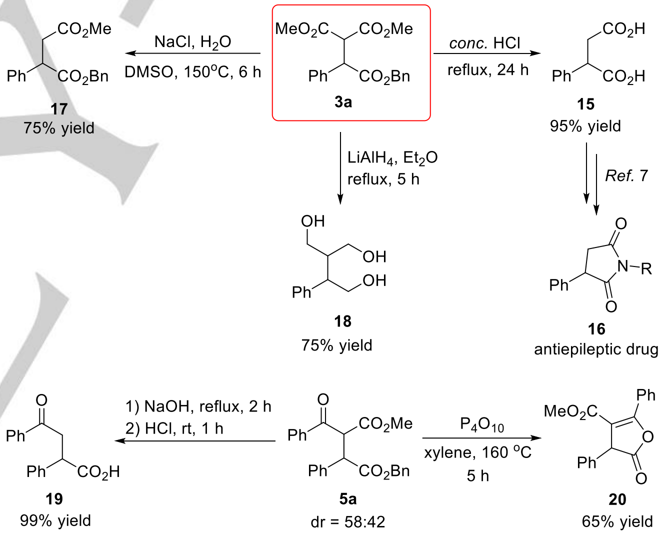
Figure 1. Relationship between the degree of enolization and the reaction rate of β-ketoesters.



Scheme 4. Proposed reaction mechanism

Based on the above investigations and the mechanistic studies in the literatures,[2f,2g,2i,6] we speculated the insertion reaction undergoes through a cyclopropanol intermediate **13**, which is formed by a copper-carbene insertion into the enol of the carbonyl substrates. The intermediate **13** is a typical donor-accepter cyclopropane and easily proceeded ring-opening/protonation reactions[7] (Scheme 4). The regioselectivity of the ring-opening of cyclopropane intermediate **13** is most likely determined by the relative polarity of the C-C bonds a and b. The by-products **6** and **7** were formed through the following possible pathways: enol intermediate reacts with copper-carbene to generate ylide **14**, which forms cyclic by-product **6** through an intramolecular nucleophilic substitution or forms O–H insertion product **7** through 1,2-proton shift. An alternative mechanism involving nucleophilic addition of enol to copper-carbene, followed by a 1,4-proton shift to afford the formal C–H bond insertion product cannot be ruled out at current stage.

The multifunctional formal C–H bond insertion products have wide applications in organic synthesis. For instance, the succinic acid derivatives have been used in the synthesis of antiepileptic drugs,[8] antiherpesvirus drugs,[9] herbicides,[10] as well as norsteroids.[11] To further demonstrate the potential applications of current method, we made diverse transformations of the C–H bond insertion products (Scheme 5). The product **3a** was readily converted to α-phenyl succinic acid **15** and diesters **17** with good to high yields by hydrolysis and decarboxylation. α-Phenyl succinic acid **15** could be converted to antiepileptic drugs **16** according to the reported process.[8] Treatment of **3a** with LiAlH$_4$ in THF produced triol **18** in 75% yield. Hydrolysis and decarboxylation of another formal C–H insertion product **5a** afforded γ-ketoacid **19** in 99% yield. Enol lactone **20** could be acquired in 65% yield when **5a** was treated with P$_2$O$_5$ at 160 °C.



Scheme 5. Transformations of C–H bond insertion products.

Conclusions

In conclusion, we developed a new and efficient catalyst system, CuCN/PCy$_3$/NaBAr$_F$, for the metal carbene formal insertion into electron-deficient C–H bonds of 1,3-diesters, *β*-ketoesters, 1,3-diketones, *β*-carbonyl nitriles and malononitriles. The reaction provided a straightforward approach to the multi-substituted succinic acid derivatives. The mechanistic studies suggested that this formal C–H bond insertion reaction likely proceeds through a cyclopropanation/ring opening reaction sequence.

Acknowledgements

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Keywords: Copper catalysts • phosphine ligands • C-H bond insertion • diazo compounds • succinic acid derivatives

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[5] CCDC 1887749 (**5e**), CCDC 1887752 (**12a**) contain the supplementary crystallographic data for corresponding products. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data request/cif. See SI for details.

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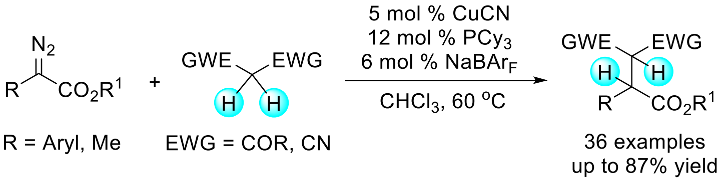
Table of Contents



A formal carbene insertion into electron-deficient C–H bonds of 1,3-diesters, β-ketoesters, β-ketonitriles, and malononitriles was realized by using CuCN/PCy_3 as a catalyst. The reaction provides a straightforward approach to the multi-substituted succinic acid derivatives. The mechanistic studies suggested that this formal C–H bond insertion reaction likely proceeds through a cyclopropanation of enol and a ring opening reaction sequence.