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Copper(I)-catalyzed highly enantioselective [3 + 3]-cycloaddition of γ-alkyl enoldiazoacetates with nitrones†

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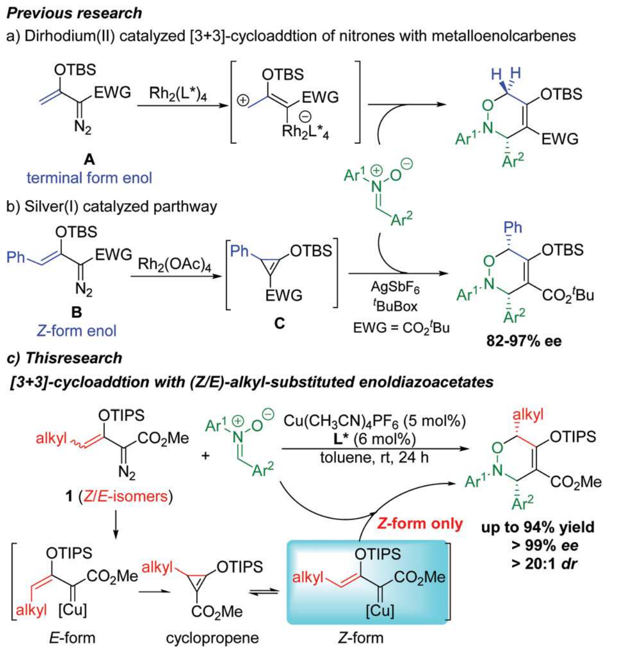
Chiral copper(I) catalysts are preferred over chiral dirhodium(II) catalysts for [3 + 3]-cycloaddition reactions of γ-alkyl-substituted enoldiazoacetates compounds with nitrones. Using the In-SaBox ligand these reactions effectively produce *cis*-3,6-dihydro-1,2-oxazine derivatives under mild conditions in high yield and with exceptional stereocontrol, and enantioselectivity increases with the size of the γ-substituent. Mechanistic studies show that cycloaddition occurs solely through the formation of (*Z*)-γ-substituted metallo-enolcarbene intermediates that are catalytically gennerated from both (*Z*)- and (*E*)-γ-substituted enoldiazoactates *via* donor–acceptor cyclopropene intermediates.

Introductions

1,3-Dipolar cycloaddition reactions of alkenes with nitrones have a long history since their first discovery by Huisgen.[1] Extensively reviewed[2] and later developed into an asymmetric catalytic methodology[3] for the synthesis of isooxazolidine derivatives, this [3 + 2]-cycloaddition has been extensively employed with and without catalysis for inter- and intramolecular reactions.[4] By comparison, scarce attention was given to [3 + 3]-cycloaddition reactions of nitrones[5] until the discovery that metallovinylcarbenes generated from enoldiazoacetate **A** not only underwent cycloaddition to form 3,6-dihydro-1,2-oxazines in good to high yields, but could do so with good enantiocontrol (Scheme 1a).[6] These reactions were performed with chiral dirhodium(II) carboxylate catalysts, but when enoldiazoacetate **B** was substituted with a phenyl group at the γ-position, the rhodium(II) catalyzed cycloaddition with nitrones did not occur; instead, rhodium catalysis efficiently converted **B** to stable donor–acceptor (D–A) cyclopropene **C** (Scheme 1b),[7] which was unreactive towards rhodium(II) catalysts. However, silver(I) catalysis using a simple *t*BuBox ligand allowed [3 + 3]-cycloaddition to occur in high yield and with high enantiocontrol using the *tert*-butyl ester of **B** and afforded the 6-phenyl-3,6-dihydro-1,2-oxazine products with exclusive *cis*-selectivity (Scheme 1b).[8] In comparison, copper(I) catalysis with the *t*BuBox ligand showed sluggish reactivity and low to negligible enantiocontrol under the same conditions, so we turned our attention to enoldiazoamides and discovered that with a modified Box ligand exceptionally high yields and enantioselectivities were obtained.[9] What has been missing from this overall survey was determination of the influence of γ-alkyl substituents on yields and selectivities in [3 + 3]-cyclo-



Scheme 1 Catalytic divergent transformations of enol diazo compound and nitrone.

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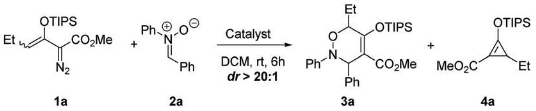
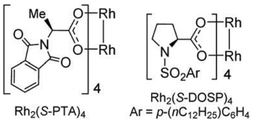
addition reactions with nitrones. Initial investigations with the γ-phenyl substituted enoldiazoacetates were discouraging.[8] Dirhodium(II) catalysis appeared to be ineffective, and copper (I) catalysis was reported to be slow and lacking enantioselectivity with chiral Box ligands. The methyl ester of **B** provided significantly lower enantiocontrol than did its *tert*-butyl ester. Dinitrogen extrusion initially forms the corresponding donor–acceptor cyclopropene that may or may not be resistant to formation of the metallovinylcarbene. Furthermore, access to γ-substituted enoldiazoacetates appeared to be contingent on the discovery of a methodology to selectively form the *Z*-isomer, rather than a mixture of both *Z*- and *E*-isomers.[10] Different reactivities and selectivities were revealed in reactions of the *E*- and *Z*-geometrical isomers.[11] Herein, we report the use of a cyclopropane-based bis-oxazoline ligand that provides high enantioselectivity and diastereoselectivity in copper (I)-catalyzed [3 + 3]-cycloaddition reactions of the methyl esters of γ-substituted enoldiazoacetates with nitrones under mild conditions. In addition, we also found that the easily prepared combination of (*E*)- and (*Z*)-γ-substituted enoldiazoacetates gave the same stereochemical outcome under these conditions because their mutual D–A cyclopropene intermediates produced only the (*Z*)-metalloenolcarbene (Scheme 1c).

Table 1 Catalyst screening in [3 + 3]-cycloaddition of enoldiazoacetate **1a** with nitrone **2a**[a]



Entry	Catalyst (x mol %)	Conv.[b] (%)	Yield[c] (%) **3a**/**4a**
1	$Rh_2(OAc)_4$ (1)	45	31/21
2	$Rh_2(oct)_4$ (1)	60	41/33
3[d]	Rh_2(*S*-DOSP)$_4$ (1)	30	21/38(0)
4[d]	Rh_2(*S*-PTA)$_4$ (1)	30	18/23(13)
5	$Cu(CH_3CN)_4PF_6$ (5)	>95	94/10
6	AgOTf (5)	>95	87/<5
7	$[Au(JohnPhos)(CH_3CN)]SbF_6$ (5)	>95	85/<5

[a] Reactions were carried out at room temperature on a 0.10 mmol scale of nitrone **2a** with 0.12 mmol of enoldiazoacetate **1a**. [b] The conversion were determined by ^1H NMR of crude reaction mixture by using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yields after flash-chromatography are reported. [d] Enantiomeric excess determined using a Daicel Chiralpak AD-H column is shown in parentheses.



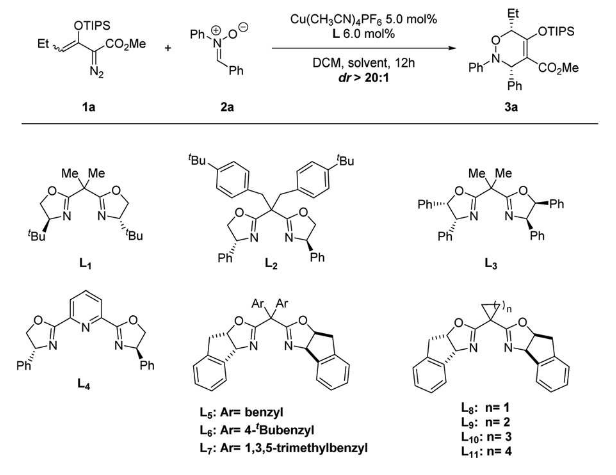
Results and discussion

Based on our previous reports, chiral dirhodium(II) tetracarboxylates and Cu(I)/Box complex were the most efficient catalytic systems in [3 + 3]-cycloaddition reactions of γ-unsubstituted enoldiazo compounds with nitrones. We selected methyl (*Z*)-3-(triisopropylsiloxy)-2-diazo-3-hexenoate (**1a**), prepared from methyl 3-oxo-2-diazohexanoate with greater than a 20 : 1 (*Z*) : (*E*) ratio,[10] for initial reactions; and we began our investigation by comparing the performances of Rh (II) and Cu(I) catalysts (Table 1). Dirhodium tetrakis(carboxylates) [$Rh_2(OAc)_4$ and $Rh_2(oct)_4$] formed the [3 + 3]-cycloaddition product **3a** in poor yields due to low conversion (entries 1–2), albeit as only the *cis*-diastereomer. Cyclopropene **4a** was obtained as a by-product along with large amounts of unreacted **2a**. What's more, with chiral dirhodium(II) tetrakis (carboxylates) [Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTA)$_4$], not only were product yields low, but **3a** was formed with no or very low enantioselectivity. However, a high yield of **3a** (up to 94%) with a limited amount of D–A cyclopropene **4a** was achieved with the use of $Cu(MeCN)_4PF_6$ (entry 5). Other catalysts, specifically cationic Au(I) and Lewis acidic Ag(I) also underwent smooth conversion of **1a** to **3a** (entries 6–7) in comparable yield but without evidence of **4a**. Notably, all these catalysts give the [3 + 3]-cycloaddtion product **3a** with a single diastereoisomer (dr > 20 : 1).

Encouraged by the outcome with $Cu(MeCN)_4PF_6$ and the observed high diasterocontrol in the formation of **3a**, we surveyed a library of chiral Box ligands (Table 2) for high enantioselectivities, which included those that had already proven their effectiveness in cycloaddition reactions with enoldiazo compounds.[12] A systematic inspection of bidentate (bis-oxazoline) **L1** and **L2**, double-side arm bisoxazoline (sabox) ligands **L3** and **L5**, and tridentate (pybox) **L4** in the reaction of **1a** with phenylnitrone **2a** revealed that **3a** was generated in only low to moderate enantiomeric excesses, but with product yields above 89% (entries 1–5). However, BnIn-SaBox **L5** showed excellent yield and enantioselectivity compared to the others. Further ligand screening found that more sterically encumbered aryl groups on the In-SaBox ligand didn't provide further improvement (entries 6–11). However, cyclopropyl-In-SaBox **L8** stood out as the superior choice (entry 8) with **3a** formed in 93% yield with 85% ee. This ligand increases the bite angle for bis-oxazoline association[13] with copper(I) and, as can be seen from results with ligands having larger ring sizes (**L9–L11**), there is a large drop in enantioselectivity as the bite angle is decreased without a change in product yield. Further optimization with solvents (entries 12–13) using **L8** revealed that reactions in toluene were slower and gave the highest yield and enantioselectivity (94% with 93% ee). Decreasing the reaction temperature to 0 °C resulted in a decrease in yield and enantioselectivity, even though the reaction time was extended to 3 days to achieve full conversion (entry 14).

With the optimized reaction conditions in hand, the applicability of this protocol was extended to a variety of γ-substituted enoldiazoactates **1** and nitrones **2**. As can be seen in Table 3, a series of nitrones **2** bearing electron-neutral, -rich, or -deficient substituents on the aryl group reacted with **1a** smoothly to give the corresponding products in high yields (86–93%) and with high enatioselectivities (91–96% ee, **3a–3g**).

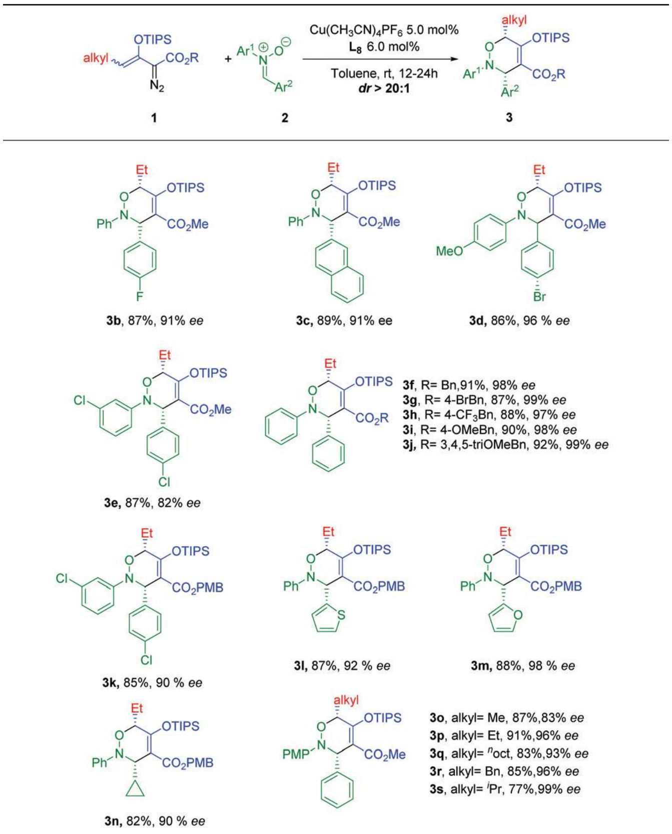
Table 2 Chiral ligand optimization[a]



Entry	Ligand	Solvent	Yield[b] (%)	ee[c] (%)
1	L_1	DCM	93	−20
2	L_2	DCM	89	10
3	L_3	DCM	91	51
4	L_4	DCM	89	9
6	L_5	DCM	92	71
6	L_6	DCM	90	60
7	L_7	DCM	90	23
8	L_8	DCM	93	85
9	L_9	DCM	95	60
10	L_{10}	DCM	93	55
11	L_{11}	DCM	92	16
12	L_8	$CHCl_3$	95	91
13	L_8	Toluene	94	93
14[d]	L_8	Toluene	89	90

[a] Reactions were carried out on a 0.10 mmol scale of nitrone **2a** with 0.12 mmol of enoldiazoacetate **1a**. [b] Isolated yields. [c] Enantiomeric excesses were determined using a Daicel Chiralpak AD-H column. [d] The reaction was performed at 0 °C for 3 days.

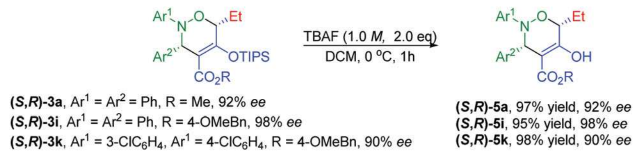
Table 3 Copper-catalyzed [3 + 3]-cycloaddition of γ-substituted enoldiazoacetates **1** with nitrones **2**: substrate scope.[a,b,c]



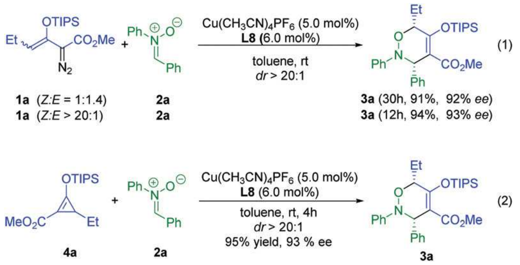
[a] All reactions were carried out on a 0.20 mmol scale in 4.0 mL of toluene: the copper(I) catalyst consisting of 5 mol% of $[Cu(CH_3CN)_4]PF_6$ and 6 mol% of chiral ligand was stirred in 2.0 mL of toluene at room temperature, and then **2a** (0.20 mmol) and **1a** (0.24 mmol) were added in sequence. [b] Isolated yields after flash chromatography. [c] Enantiomeric excesses were determined by HPLC analysis on a chiral column.

Moreover, **1** with benzyl ester groups (**3f–3g**) also gave high yields (up to 92%) with excellent enatioselectivities (>97% ee), without any adverse effect on reactivity or selectivity due to electronic or steric influences from the benzyl ester. 4-Methoxybenzyl (PMB) enoldiazo esters exhibit exceptionally high enantiocontrol compared to their methyl ester analogues (compare **3k** with **3e**), although product yields show only slight differences (87% *vs.* 85%). Because of this, the PMB substituted diazo compound was chosen for further studies. Heterocyclic substituted nitrones like 2-thiophenyl (**3l**) and 2-furyl nitrone (**3m**) also delivered the desired products with isolated yields above 87% and up to 98% ee. When the *N*-phenylnitrone with a *C*-cyclopropyl group was used, the 3,6-dihydro-1,2-oxazine cycloaddition product (**3n**) was obtained in good yield (82%) with high enantiocontrol (90% ee). Interestingly, modification of the size of the aliphatic group at the γ-position of enoldiazoacetates **1** led to an improvement in enantioselectivities of reactions with the more sterically encumbered substituents [87% yield, 83% ee (Me, **3o**) to 86% yield, 99% ee (^{i}Pr, **3s**)]. The introduction of ethyl, octyl and benzyl substituents resulted in similar product yields (85–91%), and excellent enantioselectivities (93–96% ee). These results suggest a significant influence by the γ-substituent on enantiocontrol for cycloaddition, and its absolute configuration was determined by comparison of the sign of optical rotation with previously reported [3 + 3]-cycloaddition products to be (3*S*,6*R*).[10] For further applications, the TIPS protective group is removed nearly quantitatively with TBAF to form the enol tautomer without losing enantiocontrol (Scheme 2).

To gain insight into the reaction mechanism, control experiments were carried out (Scheme 3). We first established



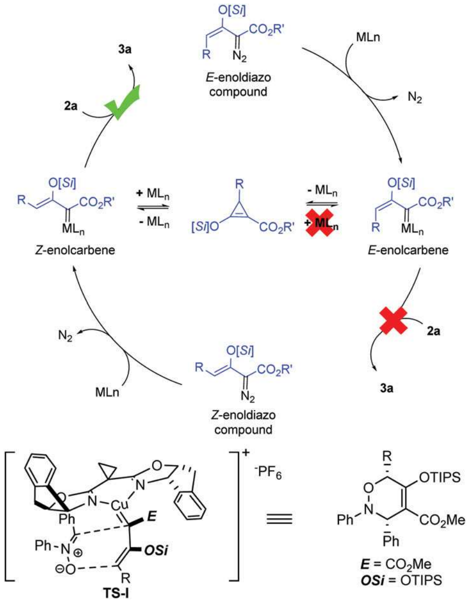
Scheme 2 TIPS-Group removal.



Scheme 3 Control experiments between Z/E-**1a** and D–A cyclopropene **4a**.

the stereochemical outcome of both (*E*)- and (*Z*)-γ-substituted enoldiazoacetate isomers. Using the reaction of a nearly equal mixture of the methyl esters of (*E*)- and (*Z*)-γ-ethylenoldiazoacetate **1a** with nitrone **2a** under the standard reaction conditions, over a longer time (30 h) this mixture gave the same yield and stereoselectivities as did γ-ethyl enoldiazoacetate **1a** having a $Z:E$ ratio greater than 20 : 1 (eqn (1)). The longer reaction time was necessitated by the significantly slower rate for dinitrogen extrusion by (*E*)-**1a**. Preliminary results (Table 1) suggested the involvement of D–A-cyclopropenes in the formation of cycloaddition product. So, in a separate experiment D–A cyclopropene **4a**[14] was used instead of **1a** and resulted in the formation of **3a** with the same enantioselectivity (eqn (2)). These results confirmed that cycloaddition resulted solely from the (*Z*)-metalloenolcarbene that was formed from the intermediate D–A cyclopropene and that the initially-formed (*E*)-metalloenolcarbene formed the D–A-cyclopropene at a much faster rate than cycloaddition with the reactant nitrone.

Based on above results and previous reports, a plausible reaction mechanism is proposed in Scheme 4. Both (*Z*/*E*)-γ-substituted enoldiazoactates undergo diazo decomposition in the presence of metal catalyst to give the corresponding metalloenolcarbene intermediates. However, the (*E*)-metalloenolcarbene intermediate does not react with the nitrone to give [3 + 3]-cyclization products, but instead closes intramolecularly to form the corresponding D–A cyclopropene (which is unreactive towards further reaction with dirhodium(II) catalysts). With copper(I), silver(I), and gold(I) catalysts the D–A cyclopropene generates only the (*Z*)-metalloenolcarbene intermediate and then undergoes [3 + 3]-cycloaddition to form *cis*-3,6-dihydro-1,2-oxazine products and predominantly one enantiomer with the suitable selection of chiral ligand.



Scheme 4 Proposed reaction mechanism.

Conclusions

In summary, the [3 + 3]-cycloaddition reaction of γ-alkyl-substituted enoldiazoactates with nitrones occurs in high yields, diastereoselectivity, and enantioselectivities using chiral bisoxazoline-ligated copper(I) catalysts with the cyclopropyl-In-SaBox **L8** ligand. In contrast to the silver(I) catalyzed reactions, where the *tert*-butyl ester was required for very high enantiocontrol,[8] the methyl esters of γ-alkyl-substituted enoldiazoactates were suitable for high enantioselectivities. Mechanistic studies confirm that the D–A cyclopropene plays key role in the formal [3 + 3]-cycloaddition reaction. (*E*)-γ-Substituted enoldiazoacetates do not undergo cycloaddition reactions unless they form D–A cyclopropene intermediates that generate only (*Z*)-metalloenolcarbene intermediates. Investigations of further applications of (*Z*)-metalloenolcarbene intermediates are underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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