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Catalyst Choice for Highly Enantioselective [3 + 3]-Cycloaddition of Enoldiazocarbonyl Compounds

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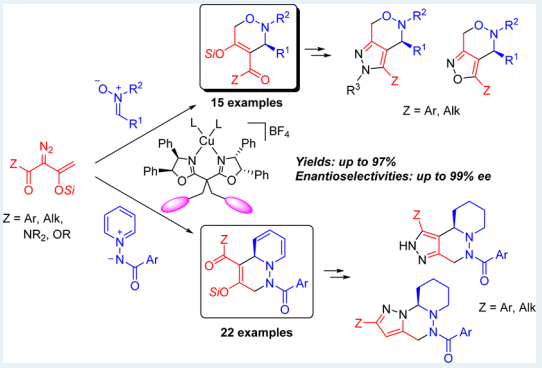
Supporting Information

ABSTRACT: Chiral copper(I) catalysts are preferred over chiral dirhodium(II) catalysts for [3 + 3]-cycloaddition reactions of enoldiazocarbonyl compounds with nitrones and acyliminopyridinium ylides, forming chiral oxazines and pyrazines in very high yield and enantioselectivity. Yields and stereoselectivities from reactions of enoldiazoketones are virtually the same as those from the corresponding esters and amides, but products from enoldiazoketones are precursors to chiral 1,3-dicarbonyl derivatives that provide additional opportunities in heterocyclic synthesis through the formation of pyrazoles and isoxazoles.



KEYWORDS: *cycloaddition, metal carbene, copper, bisoxazoline ligands, heterocycles*

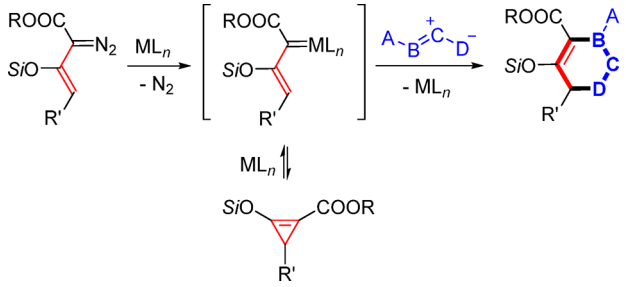
INTRODUCTION

Cycloaddition reactions have a long held and privileged position in synthetic organic chemistry.[1,2] Their applications enable the synthesis of carbocyclic and heterocyclic compounds by processes that are concerted or stepwise, and they involve the combination of *m* atoms with *n* atoms to provide a cyclic array of (*m* + *n*) atoms, where *m* and *n* are integers. For the synthesis of six-membered ring compounds, the [4 + 2]-cyclization has been the most used methodology,[3,4] but recently, [3 + 3]-cycloaddition has offered a highly selective alternative.[5] The transition metal catalyzed [3 + 3]-cycloaddition of enoldiazoacetates introduced for the first time in 2011[6] has provided high yields and good to excellent enantiocontrol in reactions with a wide variety of dipolar reagents that occur under mild conditions using dirhodium carboxylate catalysts (Scheme 1).[5,7]

An unexpected complication arose with the use of enoldiazoacetates in that their catalytic dedinitrogen conversion to the corresponding cyclopropenes[8] occurred at a faster rate than cycloaddition, but these donor−acceptor cyclopropenes also served as progenerators of the metal carbene responsible for cycloaddition.[9] The reversible formation of these cyclopropenes allows them to serve as the resting state for the metal carbene intermediate.

More recently, we have found that yields and selectivities for [3 + 3]-cycloaddition to nitrones could be increased if enoldiazoacetamides were used in place of enoldiazoacetates.[10b] Yields greater than 90% with enantioselectivities above 93% characterized reactions catalyzed by copper(I) with a chiral bisoxazoline (box) ligand. Was this an isolated improvement or was it an indication that chiral copper(I) catalysts could replace those of dirhodium(II) for cycloaddition, and could enoldiazoketones and enoldiazoacetamides be as effective as enoldiazoacetates for highly selective cycloaddition reactions? We report now that chiral copper(I) catalysis is the most effective (yield and selectivity) for cycloaddition reactions of enoldiazocarbonyl compounds that are ketones, acetate esters, and carboxamides with nitrones and acyliminopyridinium ylides, and the most suitable chiral box ligand for high yield and enantiocontrol has been identified. Furthermore, cycloaddition products from reactions with

Scheme 1. [3 + 3]-Cycloaddition of Metallo-Enolcarbenes with Dipolar Reagents



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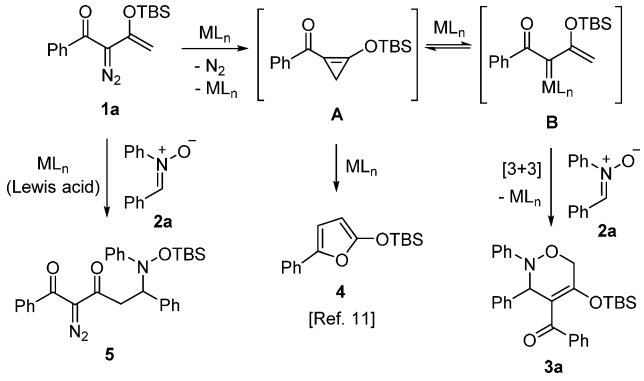
enoldiazoketones are easily converted to pyrazoles and isoxazoles with retention of stereochemistry.

RESULTS AND DISCUSSION

Selectivity. We began our investigation by asking the question: is there a general catalyst that can provide high yields and enantioselectivities of [3 + 3]-cycloaddition products for any type of enoldiazocarbonyl compounds: ester, amide, and ketone? Whereas enoldiazoacetamides are more stable than enoldiazoacetates for dinitrogen extrusion and for metal carbene or donor−acceptor cyclopropane stability, enoldiazoketones were expected to be less stable. The initial assessment of catalyst effectiveness and efficiency was performed on reactions of enoldiazoketone **1a** (previously unreported substrates for [3 + 3]-cycloaddition) with nitrone **2a** using Rh, Cu, and other metal catalysts (Table 1).

Table 1. Catalyst Screening in [3 + 3]-Cycloaddition of Enoldiazoketone 1a with Nitrone 2a



entry[a]	catalyst	yield 3a (%)[b]	yield 4 (%)[b]	yield 5 (%)[b]
1	2 mol% $Rh_2(OAc)_4$	55	24	<5
2	2 mol% $Rh_2(oct)_4$	67	28	<5
3	2 mol% $Rh_2(cap)_4$	<5	12	<5
4	5 mol% $Pd(PhCN)_2Cl_2$	24	18	<5
5	5 mol% $Cu(MeCN)_4BF_4$	78	<5	<5
6	5 mol% $Cu(MeCN)_4PF_6$	72	<5	<5
7	5 mol% CuOTf·1/2Tol	<5	<5	77
8	5 mol% Au(JohnPhos)(MeCN)SbF_6	<5	<5	86

[a]Reactions were carried out at room temperature on a 0.10 mmol scale of **2a** with 0.11 mmol of **1a** in dichloromethane for 12 h. [b]Yields were determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

In addition to the target [3 + 3]-cycloaddition product **3a** formed from metal carbene **B** (Table 1), two other products were identified: 5-phenyl-2-siloxyfuran **4**, formed via a recently reported catalytic intramolecular rearrangement of the intermediate donor−acceptor cyclopropene **A**,[11] and the Mannich addition product **5** that is readily formed via a Lewis-catalyzed pathway.[10] Dirhodium tetrakis(carboxylates) [$Rh_2(OAc)_4$ and $Rh_2(oct)_4$] formed the [3 + 3]-cycloaddition product **3a** in only moderate yields due to competing furan formation. Dirhodium tetracaprolactamate $Rh_2(cap)_4$ and $Pd(PhCN)_2Cl_2$ were not sufficiently active to cause dinitrogen extrusion from **1a** at room temperature. Lewis acidic CuOTf·1/2Tol and cationic Au(JohnPhos)(MeCN)SbF_6 favored the Mannich reaction by activation of the nitrone for electrophilic addition.[10] The highest yields (up to 78%) of cycloaddition product **3a** were achieved with the use of Cu(I) catalysts [$Cu(MeCN)_4BF_4$ and $Cu(MeCN)_4PF_6$]. Solvent screening (see the Supporting Information) did not provide an improvement in the yield of **3a** from that in dichloromethane.

With the optimum catalyst [$Cu(MeCN)_4BF_4$] and conditions in hand, we examined enantioselectivities for cycloaddition using a library of chiral box ligands (Figure 1), that

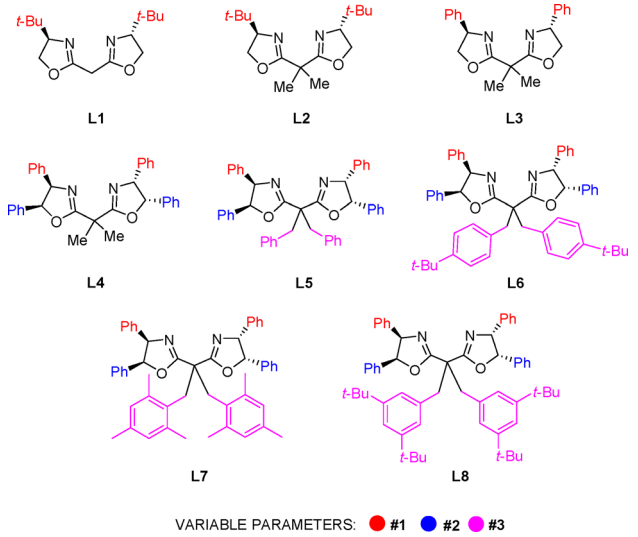


Figure 1. Library of chiral box ligands for [3 + 3]-cycloaddition of enoldiazocarbonyl compounds with nitrones.

included those that had already proven their effectiveness in the analogous reactions of nitrones with enoldiazoamides.[10b] Three variable parameters in chiral box ligands were tested to achieve maximum *ee* values in formation of **3a**: (1) disubstitution in positions 4 and 4′ of the box ligand; (2) tetrasubstitution in positions 4,4′ and 5,5′; (3) the steric bulk of side-armed substituents (sabox ligands).

All copper(I) catalysts with box ligands **L1**−**L8** showed high selectivity for [3 + 3]-cycloaddition (88−95% yield) and only trace amounts of furan **4**. The composite outcomes for yield and stereocontrol are summarized in Figure 2. The rates of [3 + 3]-cycloaddition using box ligands were faster than that without ligand, and reaction times were reduced to 4 h from 12 h with $Cu(MeCN)_4BF_4$. 4,4′-Disubstituted chiral box ligands

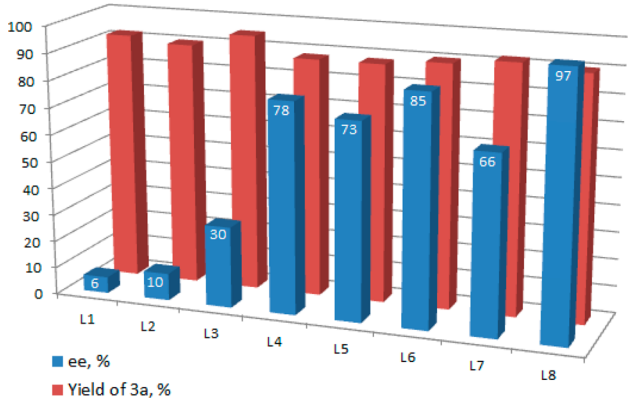


Figure 2. Catalytic effectiveness of $Cu(MeCN)_4BF_4$ with chiral box ligands **L1**−**L8** for the formation of **3a** in dichloromethane.

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with *tert*-butyl groups **L1** and **L2** did not provide noticeable asymmetric induction (*ee* ≤ 10%). However, the introduction of phenyl instead of *tert*-butyl to positions 4 and 4′ (**L3**) increased enantioselectivity to 30% *ee*, and with the 4,4′,5,5′-tetraphenylsubstituted chiral box ligand (**L4**), even higher enantioselection (78% *ee*) was obtained. On the basis of prior results from Tang and co-workers,[12] we anticipated that expanding the dihedral angle of the box ligands would lead to further increases in stereoselectivity. Indeed, use of sabox ligands **L5**−**L8**[13] resulted in further increases in stereoselectivity with **L8** being the most selective (97% *ee*) without diminished yield (90%).

Noteworthy, the use of dimethyl carbonate as a "green" solvent alternative instead of dichloromethane produced **3a** in comparable yield (92%) and enantioselectivity (94% *ee*) with sabox **L8**.

The optimal catalyst $Cu(MeCN)_4BF_4$ with **L8** was also used with the previously reported ester **6**[6] and amide **7**[10b] systems (Figure 3). This ligated Cu(I) catalyst was used for the first

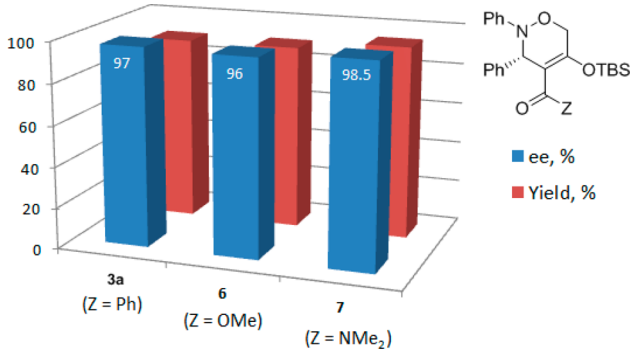


Figure 3. Influence of the Z-group on yield and selectivity of $Cu(MeCN)_4BF_4$ with **L8** in [3 + 3]-cycloaddition with nitrone **2a**.

time on enoldiazoacetate **6**, and it showed an advantage over the optimum result reported with the Rh_2(*S*-PTA)$_4$ catalyst (see Figure 4 for the structure): 96% *ee* at rt vs 93% *ee* at −30

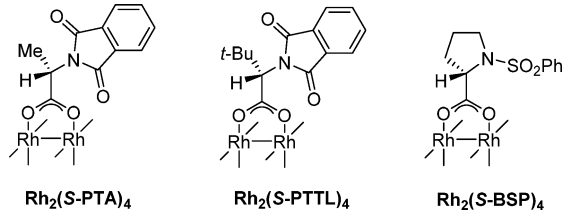
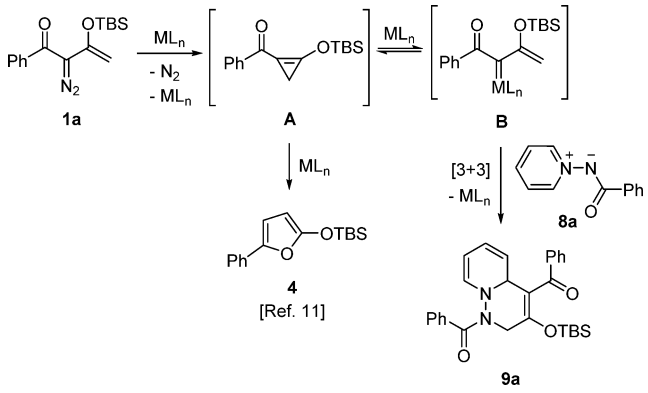


Figure 4. Structures of the most selective chiral dirhodium tetrakis(carboxylates) in enantioselective [3 + 3]-cycloaddition of enoldiazocarbonyl compounds.

°C.[6] In addition, **L8** was slightly more selective for the reaction with enoldiazoacetamide **7** (98.5% *ee*) than the reported **L4**[10b] (96% *ee*). The absence of a significant change in % *ee* with the carbonyl substituent Z indicates that Z is not in close proximity to the ligand. The absolute configuration of **3a** obtained using ligand **L8** was assigned to be (*S*) by comparison of specific rotations of **3a** with a reported amide analogue (see the Supporting Information for details).

The success achieved with nitrones prompted us to extend these studies to another stable dipolar species that had previously been investigated with chiral dirhodium(II) catalysts. Catalyst assessment from reactions of enoldiazoketone **1a** with the more basic acyliminopyridinium ylide **8a**, whose [3 + 3]-cycloaddition reactions with enoldiazoacetate esters were previously reported,[7a] is shown in Table 2.

Table 2. Catalyst Screening in [3 + 3]-Cycloaddition of Enoldiazoketone 1a with Acyliminopyridinium Ylide 8a



entry[a]	catalyst	yield **9a** (%)[b]	yield **4** (%)[b]
1	2 mol% $Rh_2(OAc)_4$	72	20
2	2 mol% $Rh_2(oct)_4$	75	22
3	2 mol% $Rh_2(cap)_4$	44	14
4	5 mol% $Pd(PhCN)_2Cl_2$	55	26
5	5 mol% $Cu(MeCN)_4BF_4$	88	<5
6	5 mol% $Cu(MeCN)_4PF_6$	84	<5
7	5 mol% CuOTf·1/2Tol	73	<5
8	5 mol% Au(JohnPhos)(MeCN)SbF_6	33	<5

[a]Reactions were carried out at room temperature on a 0.10 mmol scale of **8a** with 0.11 mmol of **1a** in dichloromethane for 12 h. [b]Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

Both [3 + 3]-cycloaddition product **9a** and furan **4** were obtained as products, and the relative amounts of the furan obtained with these catalysts was nearly the same as those in reactions with nitrone **2a**. A product from electrophilic addition to the enoldiazoketone, like the Mannich addition product formed with nitrone **2a**, was not observed.

What is striking about these results is that copper(I) catalysts do not isomerize the intermediate donor−acceptor cyclopropene **A** to furan **4**, although this compound is certainly formed in the pathway to the [3 + 3]-cycloaddition product (equilibrium between **A**/ML_n and **B**). The optimal solvent for this reaction was also dichloromethane (see the Supporting Information for solvent screening).

The same library of chiral box ligands **L1**−**L8** in combination with $Cu(MeCN)_4BF_4$ was tested for asymmetric induction in the reaction of **1a** with acyliminopyridinium ylide **8a**. Figure 5 shows that the most important parameter affecting enantioselectivity of the process is #2 (tetrasubstitution in box ligand), and there is almost no effect of parameter #3 (side arm influence). In contrast, the reaction with nitrone required both #2 and #3 parameters to achieve the highest enantiocontrol (Figure 2). Use of both **L5** and **L6** provided 96% *ee* and comparable yields (90% and 91%, respectively). **L5** was chosen for further investigations as a less expensive and lower molecular weight compound.

We have also tested a series of other chiral box ligands for the reaction of enoldiazoketone **1a** with acyliminopyridinium ylide **8a**; however, they did not provide any significant

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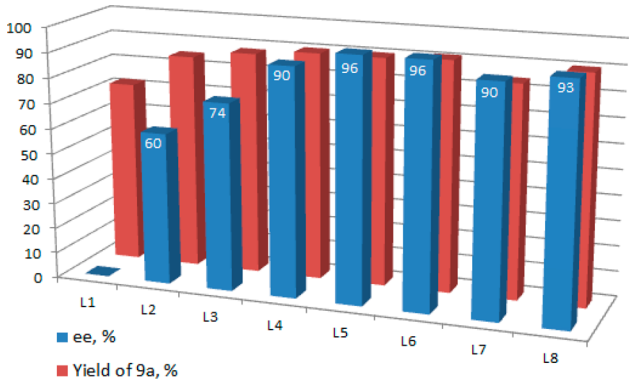

Figure 5. Catalytic effectiveness of $Cu(MeCN)_4BF_4$ with chiral box ligands **L1**–**L8** for the formation of **9** in dichloromethane.

improvement in yield and/or enantioselectivity (see the Supporting Information). In addition, extensive screening of chiral rhodium carboxylates identified the McKervey's Rh_2(*S*-BSP)$_4$ catalyst[14] (see Figure 4 for the structure), which afforded [3 + 3]-cycloaddition product **7** in 86% yield and 98% *ee*, as superior to the phthalimide-amino acid based or DOSP dirhodium(II) catalysts. Rh_2(*S*-BSP)$_4$ or Rh_2(*S*-PTTL)$_4$ catalysts afforded (*S*)-**8a** that was determined by comparison of specific rotations of **8a** with a reported ester analogue[7a] (see the Supporting Information for details), whereas "Cu(MeCN)$_4BF_4$ + **L5**" catalyst provides access to the opposite enantiomer (*R*)-**8a**.

A comparison of enoldiazo-ketone, -ester, and -amide in the reactions with **8a** (Figure 6) showed negligible differences in

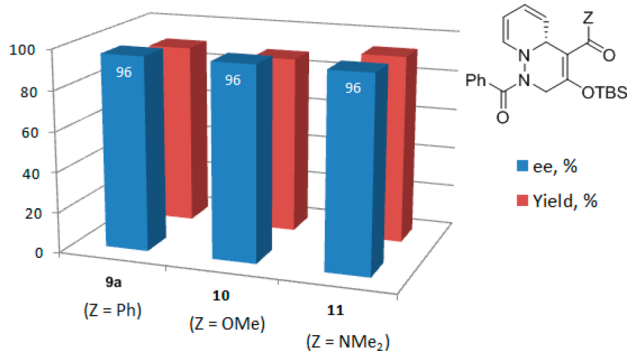

Figure 6. Influence of Z-group on the effectiveness of Cu(MeCN)$_4BF_4$ with **L5** in [3 + 3]-cycloaddition with acyliminopyridinium ylide **8a**.

enantioselectivity (96%) using $Cu(MeCN)_4BF_4$ with **L6**. However, amide **11** was formed in slightly higher yield (93%) than ester **10** (88%) or ketone **9a** (90%). Notably, this ligated copper(I) catalyst showed advantages in yield and stereoselectivity over the previously reported Rh_2(*S*-PTTL)$_4$ (see Figure 4 for the structure) for cycloaddition to form ester **10** (85% yield, 90% *ee* at 0 °C).[7a] The advantages of copper(I) catalysis for [3 + 3]-cycloaddition with enoldiazocarbonyl compounds are evident in the reactions with nitrone **2a** and acyliminopyridinium ylide **8a** (enantiocontrol, yield, absence of side reactions, especially with enoldiazoketone **1a**). To determine if the optimum ligands for cycloadditions of enoldiazoketones with dipoles **2a** and **8a** are viable with variously substituted analogues, we examined substituent effects.

Substrate Scope. The substrate scope of the reaction of enoldiazoketones with nitrones demonstrated very high efficiency of the "$Cu(MeCN)_4BF_4$ + **L8**" catalytic system. A variety of enoldiazoketones **1** and nitrones **2** were combined together to produce [3 + 3]-cycloaddition products **3** in very high yields and with excellent enantioselectivities (>90% *ee*) (Scheme 2). Both aryl and alkyl substituents in enoldiazoketones **1** were viable (Z = Ar, Alk); similar structural variations were used for nitrone **2** (R^1, R^2 = Ar, Alk). Replacement of Z = Ph with alkyl groups (methyl and *iso*-butyl) did not lower the yield of the [3 + 3]-cycloaddition products from that obtained with Z = Ph, but *ee* values were somewhat lower (**3b**,**c**). The presence of electron-donating or electron-withdrawing substituents in the aryl group of enoldiazoketone **1** (Z = Ar) did not noticeably change the stereocontrol of the copper catalyst (up to 97% *ee*, **3f**–**h**). However, the yield of compound **3f** was slightly lower (86%) due to furan formation being favored by the strongly electron-donating methoxy group. Compound **3k** with Z = 2-thiophenyl was formed with excellent yield (96%) and enantioselectivity (98% *ee*), and it was even higher than with **3a** (Z = Ph). Stereocontrol from the introduction of heterocyclic rings to the nitrone (R^2 = 2-thiophenyl, 2-furyl) was also successful (**3d** and **3e**), but the yield of **3e** was 11% lower than **3d**. We have also tested nitrones bearing alkyl substituents (R^2 = cyclopropyl or R^1 = Bn), and no limitations were observed (**3i**,**j**). Variations of EDGs and EWGs in the aromatic rings of nitrones (R^1 or R^2 = Ar) did not markedly influence catalyst effectiveness (**3l**–**o**). Only with **1f** (Z = *p*-$MeOC_6H_4$) was furan formation noticeable (9% yield). The absence of any substantial influence of these substituents on enantioselectivity suggests a 3D profile in which there is close and virtually uninhibited access of the nitrone to the enoldiazoketone.

The scope of [3 + 3]-cycloaddition reactions with acyliminopyridinium ylides **8** was also very broad (Scheme 3). As with nitrones, the same variations of substituents in enoldiazoketones **1** were used (Z = Ar, Alk). Reactions with ylide **8** tolerated any aryl substituents in the acyl group; however, cycloaddition was not limited to only the pyridinium heterocyclic ring: quinolinium and isoquinolinium rings were also used effectively. However, reactions with acetyliminopyridinium ylides led to [3 + 3]-cycloaddition products of low stability.

There was no obvious substituent effect to reaction yields and enantioselectivities on either the benzoyl group of the ylide or the enoldiazoketone (Z = Ar, Me, *iso*-Bu). Compounds **9a**–**o** were obtained in very high yields (up to 97%) and excellent enantioselectivities (>95% *ee*). The yields for methoxy-substituted compounds (**9b**,**f**,**j**,**m**) were lower (82–87%) due to competing furan formation (12% yield, for **9m**) or lower stability of the cycloaddition products (**9b**,**f**,**j**). A heterocyclic enoldiazoketone also worked well (Z = 2-thiophenyl), and [3 + 3]-cycloaddition afforded **9p** in 89% yield and 99% *ee*. As an indication of steric constraints in this transformation, the 1-naphtoyl group in ylide **8** with **1** (Z = Ph) did not form cycloaddition product **9**, but ylide **8** with **1** (Z = Me) gave product **9q** in good yield with only slightly diminished enantioselectivity (86% *ee*). Benzoyliminoquinolinium ylide was a good substrate for [3 + 3]-cycloaddition with both enoldiazoketones (Z = Ph, Me). The expected tricyclic compounds **9r** and **9s** were formed in yields >88% and up to 97.5% *ee*. The corresponding benzoyliminoisoquinolinium ylide formed **9t** in very high yield (94%) but with relatively

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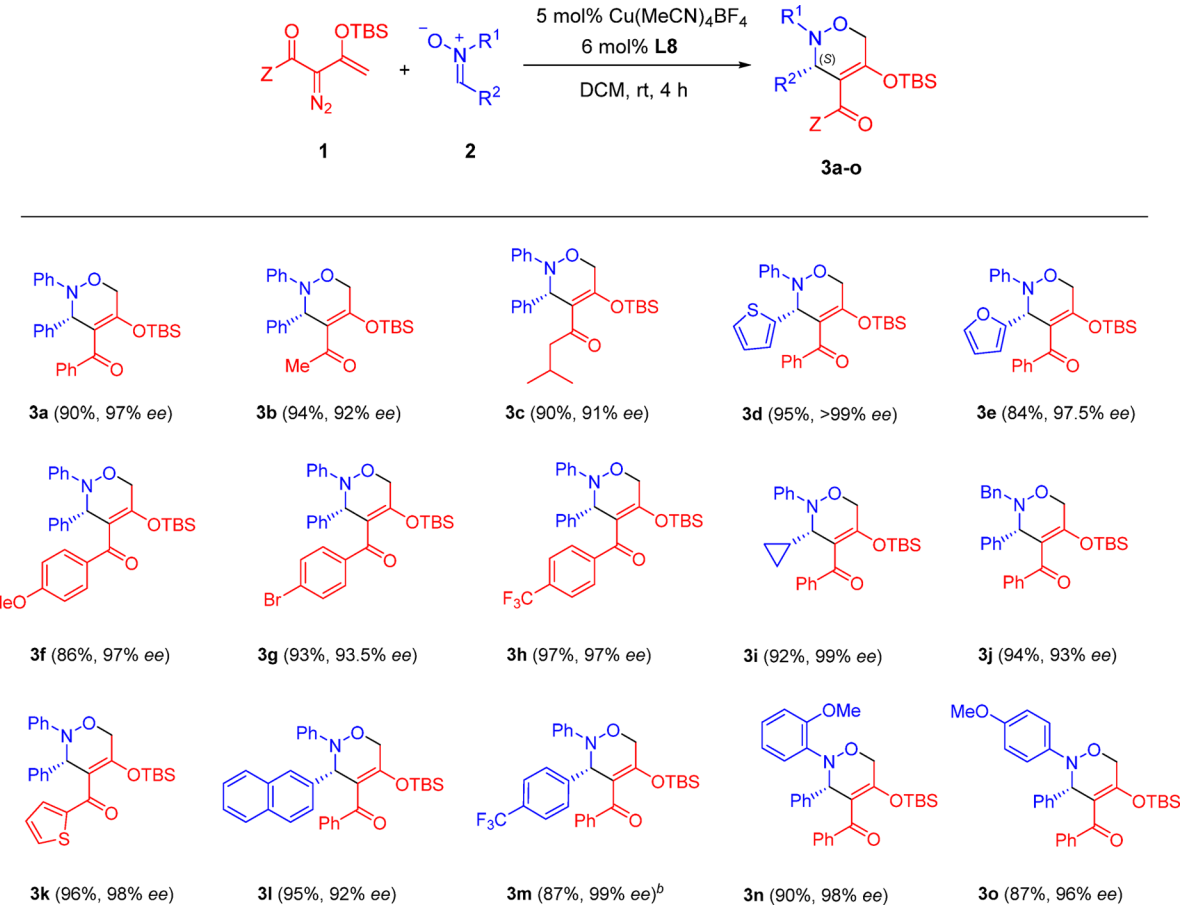
Scheme 2. Substrate Scope of the Enantioselective Copper(I)-Catalyzed Reaction of Enoldiazoketones with Nitrones[a]



[a]Reactions were carried out on a 0.20 mmol scale of nitrone **2** with 0.22 mmol of enoldiazoketone **1**. Isolated yields after flash-chromatography are reported. Enantiomeric excess was determined using Daicel Chiralpak AD-H and AS-H chiral columns. [b]Reaction time was 12 h.

low enantioselectivity (58% *ee*). With obvious steric influence, the analogous reactant with Z = Ph gave product **9** with only 4% *ee* (84% yield). For reactions of acyliminopyridinium ylides with enoldiazoamides, two examples (**11a,b**) demonstrated similar high yields and enantioselectivities.

Transformations of [3 + 3]-Cycloaddition Products. 3,6-Dihydro-2*H*-1,2-oxazines **3** are attractive molecules because of their potential utilization for further synthetic transformations,[15] and only catalytic diene-nitrosoarene Diels–Alder cycloaddition reactions offer competitive enantiocontrol.[16] Silyl deprotection on **3** by TBAF forms heterocyclic 1,3-diketones **12** in near quantitative yields (Scheme 4). As expected, these products exist in both enol- and keto-forms, and their classical transformations with hydrazines and hydroxylamine produce in high yields the corresponding pyrazoles[17] and isoxazoles,[18] compounds with a wide spectrum of biological activities,[19] that also serve as good scaffolds in drug discovery.[20]

The reaction of **12a** and **12j** with hydrazine in ethanol occurred at room temperature and afforded bicyclic pyrazoles **13** in excellent yields (up to 97%). Reductive N–O bond cleavage of **13j** using Zn/NH_4Cl produced compound **14** (86% yield), a new example of chiral 1,4-aminoalcohols attached to a pyrazole ring. The analogous reaction of **12a** with phenylhydrazine required higher temperatures (refluxed ethanol), but a single regioisomer of bicyclic *N*-phenylpyrazole **15** was obtained in 78% yield without loss of stereocontrol. The position of the phenyl group was confirmed by NMR spectroscopy using $^{15}N-^{1}H$ HMBC 2D correlation. To form the bicyclic isoxazole ring system **16**, compound **12j** was refluxed with hydroxylamine in ethanol in the presence of 10 mol% of *p*-toluenesulfonic acid (PTSA). Bronsted acid catalysis was required for formation of the C–O bond (cyclization of the intermediate oxime to oxazole ring). The structure of **12** was confirmed by NMR spectroscopy using $^{15}N-^{1}H$ HMBC 2D correlation.

Inspired by the very efficient derivatization of 3,6-dihydro-2*H*-1,2-oxazines **3**, we also explored possible transformations of the 2,4a-dihydro-1*H*-pyrido[1,2-*b*]pyridazine system **9**. Diazine structures are less well-known than are the corresponding oxazines,[21] and to our knowledge, only Tang and co-workers' chiral nickel complex-catalyzed [3 + 3]-cycloaddition of *N*-iminoisoquinoliniumylides with 1,1-cyclopropane diesters[22a] and Glorius and co-workers' NHC-catalyzed annulation reaction of enals with aromatic azomethine imines[22b] are alternative asymmetric approaches to analogous heterocyclic structures using enoldiazocompounds. We anticipated that TBAF removal of the silyl group would form the 1,3-diketone suitable for pyrazole and isoxazole synthesis. However, an unexpected complication arose upon desilylation of **9**; bicycle **9** underwent rapid aromatization-cleavage with the extrusion of pyridine and formation of acyclic **17** having extended conjugation (Scheme 5).

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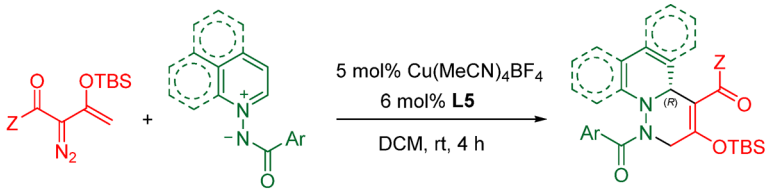
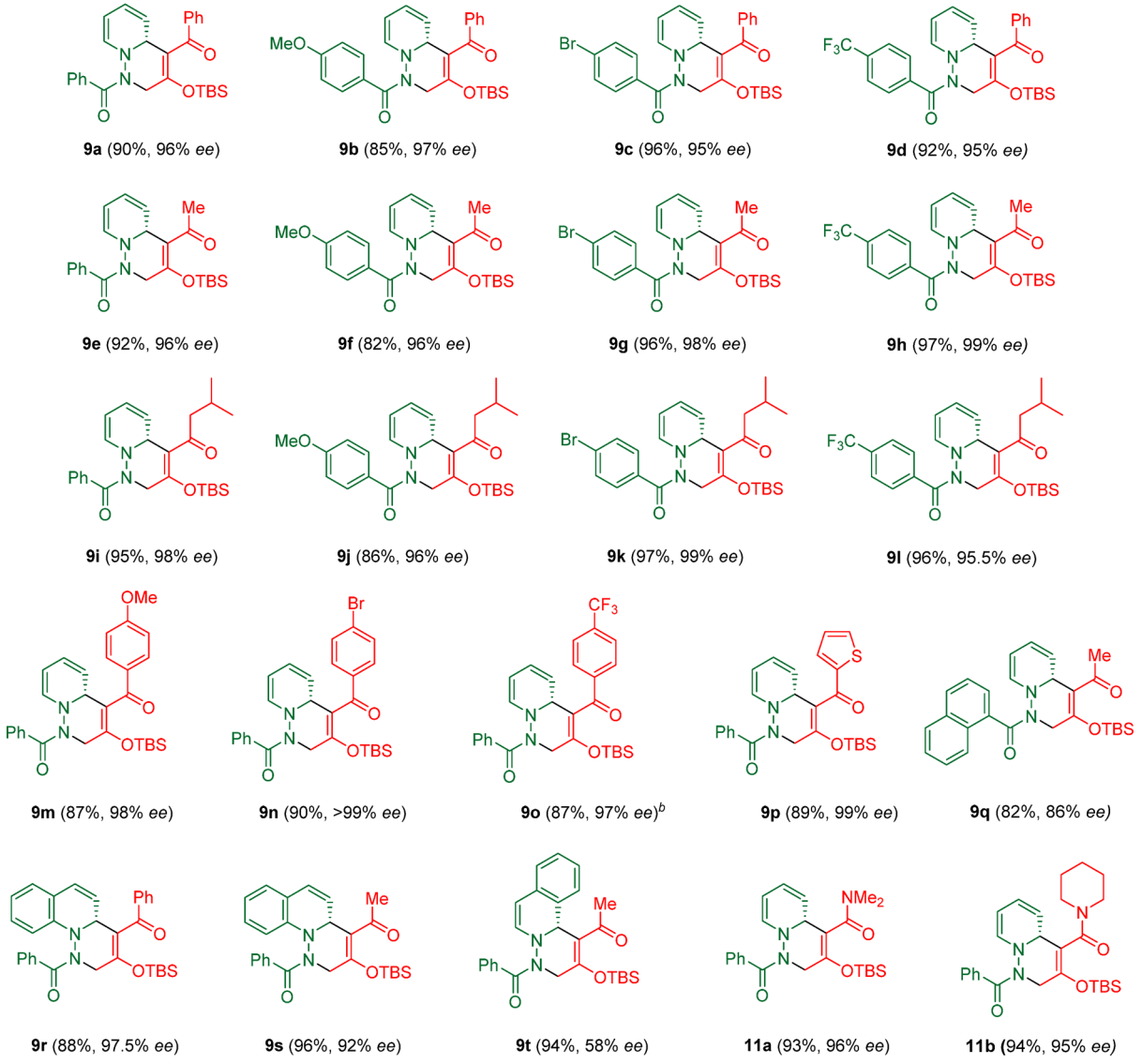
Scheme 3. Substrate Scope of the Enantioselective Copper(I)-Catalyzed Reaction of Enoldiazo-Ketones and -Amides with Acyliminopyridinium Ylides[a]





[a]Reactions were carried out at room temperature on a 0.20 mmol scale of ylide **8** with 0.22 mmol of enoldiazocarbonyl compound **1**. Isolated yields after flash-chromatography are reported. Enantiomeric excess was determined using a Daicel Chiralpak AD-H chiral column. [b]Reaction time was 8 h.

To solve this problem, we decided to stabilize this bicyclic system by palladium-catalyzed hydrogenation of the two C=C bonds of the dihyropyridine ring. The hydrogenation product **18** was obtained in 88% yield after 3 days. Treatment of **18** with TBAF retained the bicyclic system, and the corresponding bicyclic 1,3-diketone **19** was isolated in nearly quantitative yield. Cyclization of **19** with hydrazine occurred under mild conditions in the presence of 10 mol% of PTSA to form tricyclic pyrazole **20** in 80% yield. Interestingly, a side-reaction to the formation of pyrazole **20** was identified whose product formation (**21**) involved a nucleophilic attack on the tertiary C2 atom of the piperidine ring by the hydrazine nitrogen at a faster rate than attack on the second carbonyl group. Recyclization led to tricyclic pyrazole derivative **21** whose structure was confirmed by X-ray crystallography. However, a more efficient method for the synthesis of byproduct **21** was

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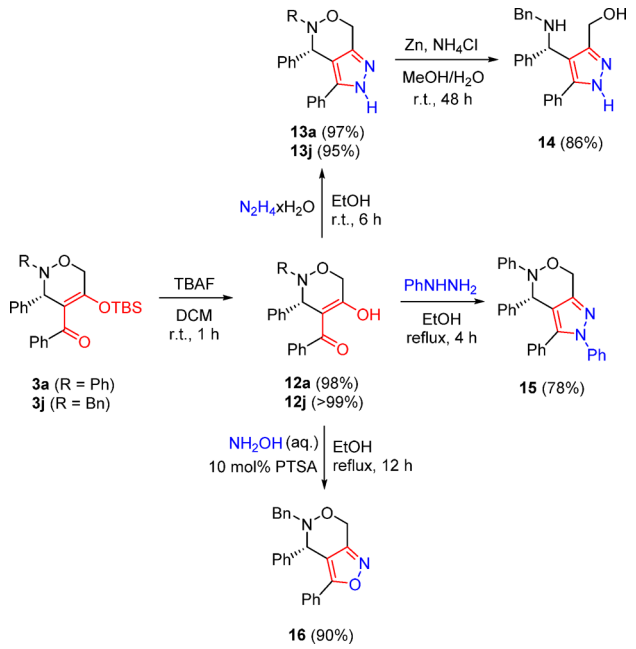
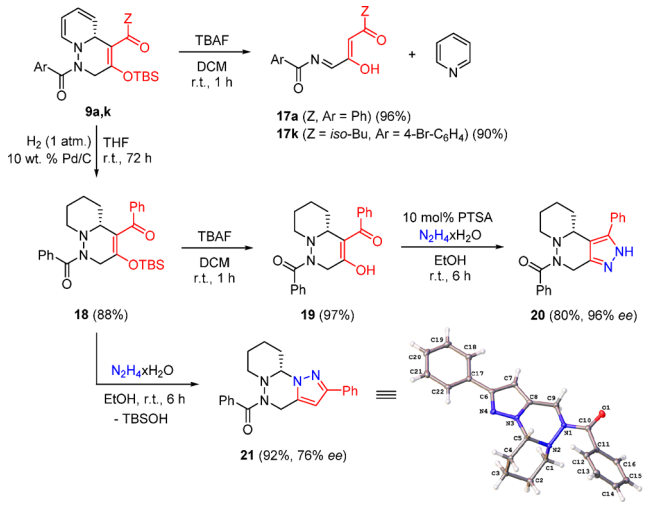
Scheme 4. Transformations of 3,6-Dihydro-2*H*-1,2-oxazine Ring System 3



Scheme 5. Transformations of 2,4a-Dihydro-1*H*-pyrido[1,2-*b*]pyridazines 9[a]



[a]X-ray structure of **21** with 50% thermal ellipsoid probability.

found: direct treatment of TBS-protected derivative **18** with hydrazine at room temperature (92% yield). However, the optical purity of **21** was 76% *ee*, decreased from 96% *ee* (**9a**) with inversion of configuration [(*R*)- to (*S*)-], suggesting a plausible mechanism of the nucleophilic substitution at C2 carbon as S_N1/S_N2. Direct treatment of **19** with hydrazine in the absence of acid was not selective, forming a mixture of **20** and **21** in a ratio of 1:2, respectively.

CONCLUSION

Copper(I) catalysts with chiral 4,4′,5,5′-tetraphenyl-sabox ligands are demonstrated to provide uniformly high enantiocontrol for [3 + 3]-cycloaddition reactions of enoldiazocarbonyl compounds with nitrone and acyliminopyridinium dipoles. The reactions with enoldiazoketones are disclosed for the first time. The similarly uniform isolated product yields using only a 10% molar excess of the enoldiazocarbonyl compound show that there is no significant competing transformation using these copper catalysts. The previous reliance on chiral dirhodium(II) catalysts is shown to be unnecessary, and in reactions with enoldiazoketones, the dirhodium catalysts are deleterious due to competing formation of the furan byproduct. However, the synthetic chiral box ligands for copper provide the opposite [3 + 3]-cycloaddition enantiomer to that from accessible phthalimide-amino acid ligated dirhodium(II) catalysts, making both enantiomers easily accessible without having to use the less available ligand enantiomers. Extensive screening of chiral box ligands for maximum % *ee* values disclosed the major factors governing enantiocontrol and directed the design of previously undisclosed sabox ligands for increased enantioselectivity. Furthermore, cycloaddition reactions of enoldiazoketones allowed easy access to 1,3-diketones that were converted to new bicyclic and tricyclic pyrazoles and isoxazoles that possess a chiral center.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b03391.

Experimental details for the synthesis and characterization of starting materials and final compounds, catalyst and solvent screening tables, copies of ^{1}H and ^{13}C NMR spectra of new compounds, HPLC traces, and crystallographic report for **21** (PDF)

Crystallographic data for **21** (CIF)

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Notes

The authors declare no competing financial interest.

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