

Copper-Catalyzed Amidation of Allylic and Benzylic C–H Bonds

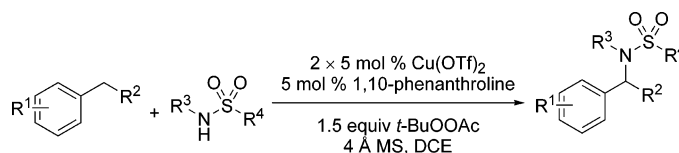
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ABSTRACT



A copper-catalyzed amidation of allylic and benzylic C–H bonds with both primary and secondary sulfonamides is described. The reaction is applicable to the coupling of a diverse set of hydrocarbon species with aryl, heteroaryl, and alkyl sulfonamides and is tolerant of a variety of functional groups. Mechanistic insight has been gained through the isolation of a benzylic acetate intermediate, which was demonstrated to undergo facile conversion to the substituted sulfonamide product under copper catalysis.

The formation of C–N bonds is of fundamental importance in organic synthesis, owing to the high prevalence of nitrogen-containing molecules of natural and pharmaceutical relevance.¹ The vast majority of techniques for the introduction of C–N bonds rely on functional group interconversions for their synthesis. In contrast, the formation of new C–N bonds directly from C–H bonds represents an extremely

attractive and efficient alternative.² Considerable achievements have been made within the past several years in order to effect amidation via a C–H activation strategy, particularly with regards to allylic and benzylic C–H bonds.^{3–7}

For example, C–H amidation methodologies that proceed through transition metal-nitrene (imido) intermediates⁸ have been demonstrated with a variety of metal catalysts, including

(1) *Modern Amination Reactions*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

(2) For a recent review of oxidative functionalization of C–H bonds, see: Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463.

(3) For some recent reviews of C–H bond amidations, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518–3520. (b) Du, Bois, J. *Chemtracts* **2005**, *18*, 1–13. (c) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed; Wiley-VCH: Weinheim, 2005; pp 379–416. (d) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657–669.

(4) Representative intramolecular metal-nitrene-type amidations: (a) Kim, M.; Muleahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199. (c) Zhang, J.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403–5408. (d) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210–4212. (e) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379. (f) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610–3619. (g) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607–1615. (h) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468. (i) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (j) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (k) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729.

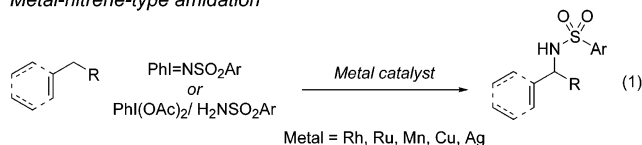
(5) Representative intermolecular metal-nitrene-type amidations: (a) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784–11791. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049. (c) Leung, S. K.-Y.; Tsui, W.-M.; Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629–16640. (d) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561–9564. (e) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339–3342. (f) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531–532. (g) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858–7864. (h) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236. (i) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087–1105. (j) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927–1930. (k) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400–1401.

(6) (a) Kohmura, Y.; Kawasaki, K.-i.; Katsuki, T. *Synlett* **1997**, 1456–1458. (b) Smith, K.; Hupp, C. D.; Allen, K. L.; Slough, G. A. *Organometallics* **2005**, *24*, 1747–1755. (c) Clark, J. S.; Roche, C. *Chem. Commun.* **2005**, 5175–5177.

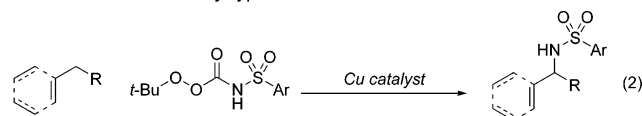
(7) For other strategies for the amination of allylic and benzylic C–H bonds, see: (a) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131–4146. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708.

(8) Review: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571–1586.

Scheme 1. Catalytic Methods for C–H Bond Amidation
Metal-nitrene-type amidation



aza-Kharasch-Sosnovsky-type amidation



rhodium, ruthenium, and manganese (Scheme 1, eq 1). Although great strides have been made in intramolecular⁴ amidation reactions, intermolecular^{4e,5} couplings remain less advanced, often requiring an excess (>5 fold) of hydrocarbon component and proceeding in poor to modest yield. Furthermore, as a consequence of their mechanism, these amidation methodologies remain restricted to the coupling of primary amide components.

An intriguing alternative to the metal-nitrene-based amidation strategies is the copper-catalyzed allylic and benzylic amidation reaction first disclosed by Katsuki and co-workers^{6a} (Scheme 1, eq 2). The reaction utilizes preformed peroxycarbamates, which serve as both the oxidant and amine component, and is based on a Kharasch–Sosnovsky reaction.⁹ Although the reaction is conceptually a powerful complement to the metal-nitrene-type amidation methods, the requirement for presynthesized, unstable peroxycarbamates, combined with the narrow substrate scope and poor yields, severely limits the synthetic utility of this process.^{6b} In addition, the course of the reaction (amidation versus oxidation) remains highly dependent on the electronic properties of the peroxycarbamate species as well as the ligand and hydrocarbon component used.^{6c}

Inspired by these efforts as well as early reports by Kharasch,¹⁰ we sought to develop a more general copper-catalyzed intermolecular amidation strategy that would be capable of coupling *both primary and secondary amide* reagents with a range of hydrocarbon species. Key to the merit of such a methodology would be the division of amide and oxidant into separate components, thereby circumventing the need for the presynthesis of unstable reagents.^{6,8}

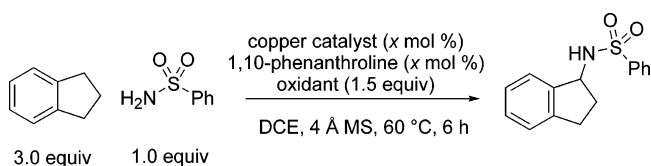
Our initial explorations focused on the intermolecular coupling reaction between indane and benzenesulfonamide (Table 1). Choice of copper catalyst¹¹ (Cu(OTf)₂) and oxidant¹² (*t*-BuOOAc) proved to be critical to the reaction

(9) (a) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845–866. (b) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567–3571. (c) Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 756.

(10) A single example of a copper-catalyzed amidation of cyclohexene with phthalimide in the presence of *tert*-butyl hydroperoxide (14% yield) was described by Kharasch almost 50 years ago: Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1958**, *23*, 325–326.

(11) Other copper catalysts including CuCl₂, Cu(MeCN)₄PF₆, Cu[BF₄]₂, and CuOTf-benzene were less effective in the amidation reaction.

Table 1. Exploration of Reaction Parameters on the Amidation of Indane with Benzenesulfonamide



entry	catalyst	ligand	oxidant	yield % ^a
1	none	5 mol %	<i>t</i> -BuOOAc	0 ^b
2	Cu(OAc) ₂ (10 mol %)	10 mol %	<i>t</i> -BuOOAc	8 ^b
3	Cu(OTf) ₂ (10 mol %)	10 mol %	<i>t</i> -BuOOH	20 ^b
4	Cu(OTf) ₂ (10 mol %)	10 mol %	<i>t</i> -BuOOBz	48
5	Cu(OTf) ₂ (10 mol %)	10 mol %	<i>t</i> -BuOOAc	49
6	Cu(OTf) ₂ (10 mol %)	10 mol %	<i>t</i> -BuOOAc [addition over 6 h]	63
7	Cu(OTf)₂ (2 × 5 mol %)	5 mol %	<i>t</i>-BuOOAc [addition over 6 h]	73
8	Cu(OTf) ₂ (2 × 5 mol %)	5 mol %	<i>t</i> -BuOOAc [addition over 6 h]	35 ^{b,c}
9	Cu(OTf) ₂ (2 × 5 mol %)	5 mol %	<i>t</i> -BuOOAc [addition over 6 h]	41 ^d

^a Isolated yield. ^b Determined by HPLC analysis versus a calibrated internal standard (average of two runs). ^c Reaction conducted at room temperature. ^d 1.0 equiv of indane was used.

efficiency. Although *t*-BuOOBz gave similar yields in the reaction of benzenesulfonamide with indane (entry 4 vs entry 5), we found the reaction of other hydrocarbon species with *t*-BuOOBz to be less general than that with *t*-BuOOAc. In addition, the acetic acid byproduct from the reaction with *t*-BuOOAc is easier to remove during the workup procedure than benzoic acid.

Further improvements in yield could be realized through slow addition of the oxidant via syringe pump over 6 h (entry 6). Finally, by adding the copper catalyst in two portions of 5 mol %, first at the start of the reaction and then after 3 h, we were able to generate the amidation product in a reasonable 73% isolated yield (entry 7).^{13,14}

With a suitable set of reaction conditions developed, we then investigated the range of sulfonamide coupling partners that could be employed (Table 2). Gratifyingly, *both primary and secondary sulfonamides* reacted with indane under the copper-catalyzed amidation procedure. This distinguishes the current methodology as one of the few allylic and benzylic C–H bond amidation processes in which secondary amide components can be employed.¹⁵

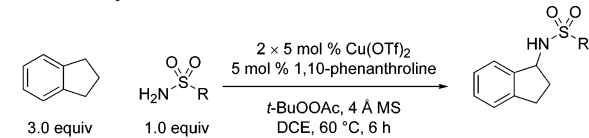
(12) Other oxidants including PhI(OAc)₂ and chloramine-T gave lower yields of product.

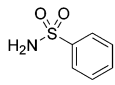
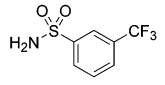
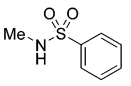
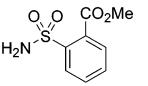
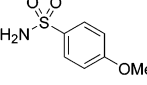
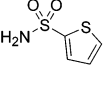
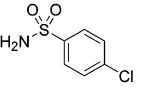
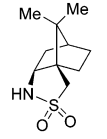
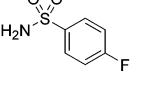
(13) Yields in the absence of 1,10-phenanthroline ligand are only slightly lower (64% by HPLC); however, use of an excess of ligand (20 mol %) results in dramatically diminished yields.

(14) We suspect the Cu(OTf)₂ catalyst may be deactivated or decomposing in the presence of an excess of the oxidant.

(15) The only other examples of similar amidation reactions with secondary amides were conducted with phthalimide¹⁰ and saccharin^{6b}.

Table 2. Copper-Catalyzed Amidation of Indane with Primary and Secondary Sulfonamides



entry	sulfonamide	yield ^a (%)	entry	sulfonamide	yield ^a (%)
1		73	6		70
2		78	7		76
3		60	8		67
4		71	9		86 ^b
5		69			

^a Isolated yield. ^b Indane product was obtained as a 1:1 mixture of diastereomers.

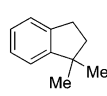
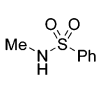
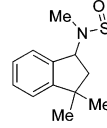

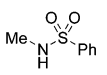
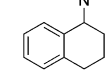

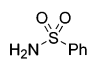
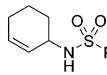

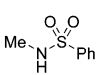
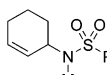

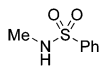
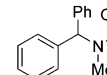
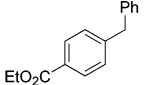
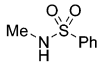
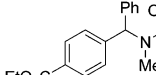

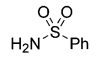
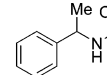
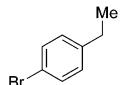
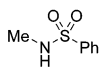
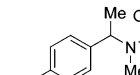
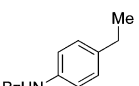
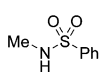
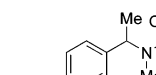

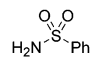
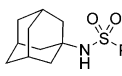
Overall, the yields remain relatively consistent with sulfonamides of varying electronic and steric properties; the electron-rich *p*-methoxybenzenesulfonamide (entry 3), the electron-deficient *m*-trifluoromethylbenzenesulfonamide (entry 6), and the *ortho*-substituted carbomethoxybenzenesulfonamide (entry 7) all yielded amidation products in 60–76% yields. Heteroaromatic 2-thiophenylsulfonamide (entry 8) was also tolerated in the copper-catalyzed amidation methodology. Finally, amidation with a chiral sultam (entry 9) proceeded in 86% yield, demonstrating that alkyl sulfonamides are also suitable reaction partners. Here, the indane product was formed as a 1:1 mixture of diastereomers that were separated by column chromatography and analyzed by X-ray crystallography to ascertain the absolute stereochemistry at the benzylic center.

Of technical significance, the reaction is operationally facile to conduct; all reagents were weighed and handled without the need for rigorous exclusion of air or moisture. In addition, few byproducts were detected in the crude reaction mixture,¹⁶ with the exception of small amounts (typically <5%) of the *N,N*-bis-indanylsulfonamide product observed in the couplings of primary sulfonamides.

The Cu(OTf)₂/*t*-BuOOAc system could also be applied to the amidation of a range of hydrocarbon species with both primary and secondary sulfonamides (Table 3). For example, the direct generation of C–N bonds in 1,1-dimethylindane (entry 1) and tetrahydronaphthalene (entry 2) occurs in reasonable yields under the general reaction conditions.

(16) For those reactions that proceeded in only moderate yield, the remaining mass balance consisted of primarily the sulfonamide and hydrocarbon starting materials.

Table 3. Copper-Catalyzed Amidation of Various Hydrocarbon Components with Primary and Secondary Sulfonamides

entry	hydrocarbon	sulfonamide	product	yield % ^a
1				63
2				54
3				75
4				61
5				50 ^b
6				47 ^b
7				60 ^b
8				49 ^b
9				64 ^b
10				56 ^{b,c}

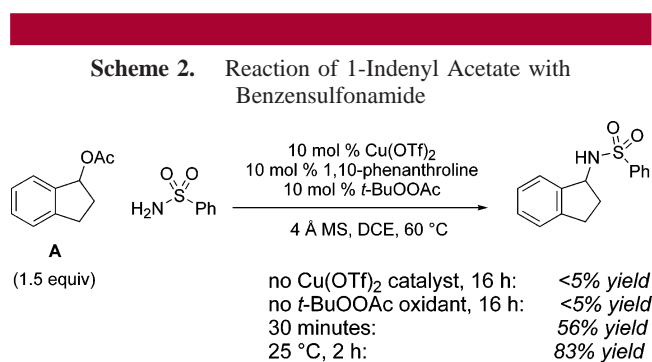
^a Isolated yield. ^b Reaction conducted at 80 °C. ^c The 2-adamantane sulfonamide regioisomer was formed in <5% yield as determined by ¹H NMR analysis.

Amidation of the allylic C–H bonds of cyclohexene was realized both with benzenesulfonamide (entry 3) and *N*-methylbenzenesulfonamide (entry 4). In contrast to several metal-nitrene-based amidation reactions,⁸ no aziridination product could be detected in the crude reaction mixture.¹⁷ The method could also be applied to acyclic hydrocarbons as well as cyclic hydrocarbons. Thus diphenylmethane (entries 5 and 6) as well as ethylbenzene derivatives (entries 7–9) serve as suitable reaction partners in this transformation. Notably, the amidation procedure tolerates a variety of functional groups on the hydrocarbon component, including an ester (entry 6), aryl bromide (entry 8), and amide (entry 9). The reaction is chemoselective for C–N bond formation

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with a secondary sulfonamide in the presence of a secondary benzamide (entry 9). Finally, amidation of the C–H bonds of adamantane could be achieved (entry 10). Here reaction occurs preferentially at the bridgehead position, affording the 1-adamantyl sulfonamide in 56% yield and greater than 95:5 regioselectivity.

Acetate **A** has been observed in minor quantities (<5% by HPLC, MS) during the course of our amidation reaction, presumably forming via a direct Kharasch–Sosnovsky reaction with the *tert*-butylperacetate oxidant. To help ascertain whether **A** is a potential intermediate in this reaction, we explored the coupling of 1-indanyl acetate **A** with benzenesulfonamide under our copper-catalyzed conditions (Scheme 2). Reaction of **A** with the sulfonamide occurs



very rapidly at room temperature within 2 h, giving an 83% isolated yield of product. This reaction does not proceed in the absence of copper, even at elevated temperatures (<5% yield). Interestingly, this coupling requires catalytic quantities of both copper and *tert*-butylperacetate oxidant in order to proceed, suggesting proper oxidation state of the copper catalyst is an important requirement for reactivity. While

these observations do not preclude a mechanistic pathway in which product formation occurs directly from the hydrocarbon species, we have demonstrated that an intermediate benzylic acetate **A** can be converted to product under the copper-catalyzed conditions.^{18,19}

In conclusion, we have demonstrated a copper-catalyzed amidation of allylic and benzylic C–H bonds with sulfonamides that tolerates functionality on both coupling partners. This methodology serves as a complement to the metal-nitrene-type amidation processes in that both primary and secondary amides can be utilized. Further investigations into more active and robust copper catalysts and extension to other amide coupling components²⁰ is ongoing.

Acknowledgment. We thank Zahir Sadikali (Merck Frosst) for conducting preliminary experiments, NSERC for an undergraduate research award to G.P., Nancy N. Tsou and Richard G. Ball at Merck Research Laboratories (Rahway) for X-ray crystallographic analysis, and the McGill University Mass Spectroscopy Unit for HRMS analysis.

Supporting Information Available: Experimental procedures and compound characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) A third mechanistic possibility involves oxidation of the hydrocarbon species to an alkene, followed by a copper-catalyzed hydroamination, although diphenylmethane and adamantane, for which alkene intermediates are unlikely, are reactive under our conditions. See: Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561–3564.

(19) To our knowledge, this copper-catalyzed amidation reaction of a benzylic acetate has not previously been observed; however, copper-catalyzed aminations of allylic halides are known. See: Baruah, J. B.; Samuelson, A. G. *Tetrahedron* **1991**, *47*, 9449–9454.

(20) Under the optimized conditions described in table 1, amidation of indane with benzamide or *tert*-butyl carbamate proceeds in only 5% and 12% yields, respectively.

Synthesis of Chiral 3-Substituted Hexahydropyrroloindoline via Intermolecular Cyclopropanation

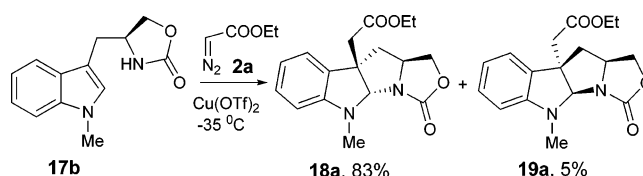
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ABSTRACT



A new and efficient synthetic route to chiral 3-substituted hexahydropyrroloindoline **18** possessing absolute configurations in accordance with indole alkaloids has been developed from readily available L-tryptophan. The key step relies on the one-pot cascade reaction of oxazolidinone **17** with diazoester, which proceeds through intermolecular cyclopropanation, ring opening, and cyclization.

The structural moiety of chiral 3-substituted hexahydropyrroloindoline is widely represented in a number of bioactive indole alkaloids such as physostigmine, pseudophrynaminol, bromoflustramide, bromoflustramine, mollenine, requafortine, ardeemin, amaumomine, and aszonalenin.¹ As an important precursor for the syntheses of these indole alkaloids, 3-substituted hexahydropyrroloindoline has attracted the intensive interest of synthetic chemists. A variety of methods have been reported for preparing racemic 3-substituted hexahydropyrroloindoline² and chiral 3-substituted hexahydropyrroloindolines, including using the catalytic asymmetric Heck reaction,³ catalytic asymmetric alkylation and allylation,⁴ chiral auxiliary induced asymmetric alkylation and

rearrangement,⁵ asymmetric addition–cyclization,^{6,7} desulfurization–cyclization,⁸ asymmetric 3,3-rearrangement,⁹ and chiral resolution¹⁰ as key steps.

We recently reported a synthesis of a pentacyclic substructure of the indole alkaloids communesin and perophora-

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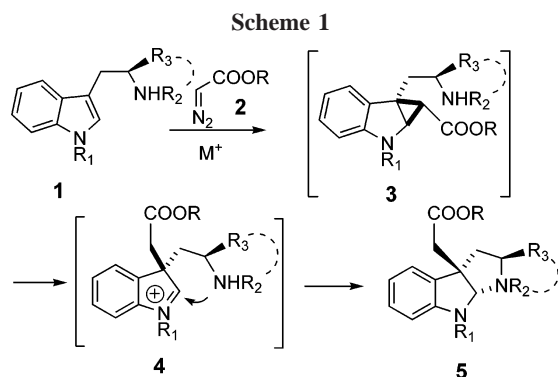
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midine that proceeded through an intramolecular cyclopropanation of tryptamine derivatives, and a ring opening of the resulting cyclopropane with an in situ generated aniline.¹¹ In continuation of our methodology development for the syntheses of other indole alkaloids, we now describe, in this paper, a new and efficient approach to chiral 3-substituted hexahydropyrroloindolines through the one-pot cascade reactions of intermolecular cyclopropanation, ring opening, and cyclization as shown in Scheme 1.



Besides generating a desirable cyclopropane ring on the 2,3-double bond of **1**,¹² there are several possible reaction pathways such as direct N–H, C–H, and C–C insertion when **1** is treated with a diazoester **2**. The feasibility of effecting the desired cascade reaction to afford the 3-substituted hexahydropyrroloindoline **5** was judged to be dependent mainly on the nature of R₁ and R₂ substituents in **1**. The formation of a cyclopropane intermediate **3** and the consecutive nucleophilic attack of the amine group on the C=N double bond of the resulting indolenium **4** after collapse of cyclopropane ring would rely on the electronic density of the 2,3-double bond and the nucleophilic addition capability of the amine group. Keeping this in mind, we first explored the effects that different R₁ and R₂ substituents would have on the reaction using *N,N'*-disubstituted tryptamine **1**.

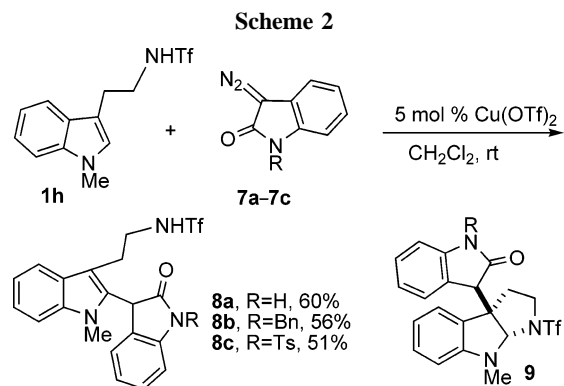
As speculated, initial experiments revealed that the substituents R₁ and R₂ had substantial effects on the reactivity of **1** under standard diazo decomposition conditions (4 equiv of **2a**, 5 mol % of Cu(OTf)₂, CH₂Cl₂, room temperature). When R₁ was an electron-donating group (R₁ = Me, Bn), the reactions of **1d** and **1e** (R₂ = Ac) with ethyl diazoacetate **2a** gave compounds **5d** and **5e** in 16% and 22% yields, respectively, as well as the C–H insertion product **6e** in less than 3% yield (Table 1, entry 5). Further screening the effect of the R₂ group in **1** showed that an electron-withdrawing

Table 1. Condition Optimization of of *N,N'*-Disubstituted Tryptamine

entry	1	R ¹	R ²	5 (%)	6 (%)
1	1a	H	Ac	5a (0)	6a (0)
2	1b	Ts	Ac	5b (0)	6b (0)
3	1c	Boc	Ac	5c (0)	6c (0)
4	1d	Bn	Ac	5d (16)	6d (0)
5	1e	Me	Ac	5e (22)	6e (3)
6	1f	Me	Bn	5f (0)	6f (0)
7	1g	Me	Boc	5g (27)	6g (0)
8	1h	Me	Tf	5h (33)	6h (0)
9	1i	Me	Ns	5i (36)	6i (0)

group for R₂ was required for a successful cascade reaction (Table 1, entries 6–9). With the strongest electron-withdrawing groups Tf and Ns (Table 1, entries 8 and 9), **5h** and **5i** were isolated in 33% and 36% yields. Compound **6** was generated either through the collapse of the cyclopropane intermediate **3** or through the direct C–H insertion of carbene at position 2 of the indole core. Besides Cu(OTf)₂, CuOTf also catalyzed the reaction to give a similar result. However, Cu(CH₃CN)₄PF₆, Rh₂(OAc)₂, and (Ph₃P)₃RhCl were inactive for the reaction. Replacement of methylene chloride with other solvents such as 1,2-dichloroethane, chloroform, nitroethane, and toluene did not significantly improve the yield of desired compound **5**.

Encouraged by the above successful one-pot cascade reaction, our efforts were next directed toward the synthesis of compound **9** possessing oxindole substituent at position 3. The latter might serve as an important intermediate in the synthesis of calycanthaceous alkaloids (Scheme 2).¹³ Un-



fortunately, when **1h** reacted with diazo compounds **7a–c**, derived from isatin, in the presence of 5 mol % of Cu(OTf)₂ in methylene chloride at room temperature, the reactions provided exclusively the C–H insertion products **8** in

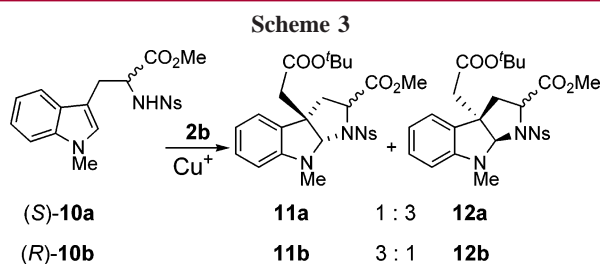
(11) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187.

(12) There were only two reports found in the literature which described the formation of a cyclopropane ring on the 2,3-double bond of simple *N*-substituted indoles by the metal catalyzed diazo decomposition reaction, see: (a) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277. (b) Welstead, W. J.; Stauffer, H. F.; Sancilio, L. F. *J. Med. Chem.* **1974**, *17*, 544.

moderate yield, instead of affording the anticipated products **9**. This was probably due to steric effects in **7**, which precluded formation of the cyclopropane ring on the 2,3-double bond of tryptamine **1h**.

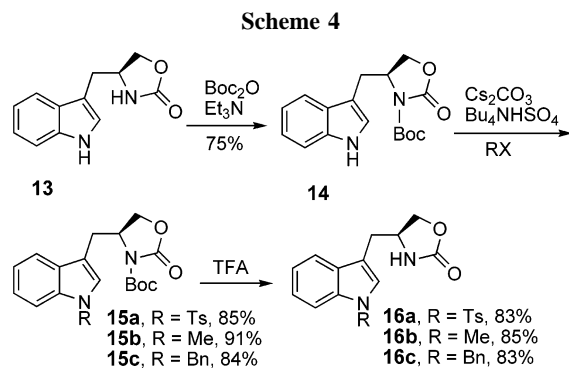
Although the yield was not that high, the one-pot cascade reaction of **1** with **2** was practical for setting up the cis-stereochemical centers at positions 2 and 3 of the indole core at the same time.

We next explored the application of our process to (*S*)-*N*-methyl-*N'*-Ns-tryptophan methyl ester **10a** derived from *L*-tryptophan (Scheme 3). When **10a** was treated with *tert*-



butyl diazoacetate **2b** under the same condition, two diastereoisomers **11a** and **12a** preferably with *endo*-selectivity^{4b} were isolated in 10% and 32% yields, respectively. The stereochemistry of **11a** and **12a** was determined by NOE experiments. The reaction of (*R*)-**10b** derived from *D*-tryptophan with **2b** gave **11b** and **12b** in 45% combined yield and a 3:1 ratio.

The low diastereoselectivity (1:3) induced by **10** was most likely attributable to the flexibility of the side chain. To improve the diastereoselectivity as well as the yield, the side chain of tryptophan was fixed as an oxazolidinone substructure. In this approach, the carbamate functional group also served as an electron-withdrawing group to enhance the nucleophilic capability of the amine group. Oxazolidinone **16** was readily prepared through a three-step route from commercially available (*S*)-**13** as shown in Scheme 4.

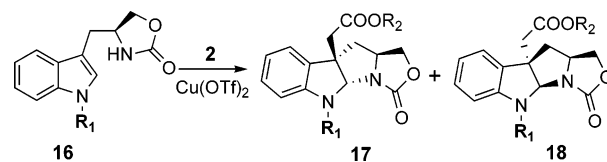


Protection of the amide group in **13** with Boc led to the formation of compound **14**. Alkylation or tosylation of **14** under phase-transfer conditions provided compounds **15a–c**

in 84–91% yield. Treatment of **15** with 20% TFA in CH₂Cl₂ afforded oxazolidinone **16** in high yield.

With indole oxazolidinone **16** in hand, we were able to test whether a side chain with a rigid carbamate functional group would improve the yield and diastereoselectivity (Table 2). It was not surprising that only the N–H insertion

Table 2.^a



entry	16	R ¹	R ²	temp, °C	tim, e h	17 (%)	18 (%)
1	16a	Ts	^t Bu	25	4	— ^b	—
2	16b	Me	Et	25	3	17a (50)	18a (35)
3	16b	Me	Et	0	5	17a (55)	18a (25)
4	16b	Me	Et	–25	7	17a (71)	18a (10)
5	16b	Me	Et	–35	30	17a (83)	18a (5)
6	16b	Me	Et	–45	30	17a (0)	18a (0)
7	16b	Me	^t Bu	25	4	17b (62)	18b (9)
8	16b	Me	^t Bu	0	6	17b (76)	18b (10) ^c
9	16b	Me	^t Bu	–5	12	17b (52)	18b (5) ^d
10	16c	Bn	^t Bu	0	30	17c (18)	18c (0) ^e
11	16c	Bn	^t Bu	–25	30	17c (0)	18c (0) ^f

^a Reactions were carried out with 4 equiv of **2** and 5 mol % of Cu(OTf)₂. ^b 66% yield of N–H insertion product and 30% yield of *O*-adduct were isolated. ^c 6% yield of N–H insertion product was isolated. ^d 7% of N–H insertion product was isolated. ^e 48% yield of N–H insertion product was isolated. ^f 30% yield of N–H insertion product was isolated, see the Supporting Information.

product and oxygen adduct were produced when **16a**, with an electron-withdrawing group on the indole nitrogen, reacted with **2b** at room temperature (Table 2, entry 1). To our delight, the *exo*-diastereoselectivity^{6a} was greatly enhanced to a 17:1 ratio when oxazolidinone **16b** (R = Me) reacted with **2a** at –35 °C, and the major isomer **17a** and minor isomer **18a** were isolated in 83% and 5% yields, respectively (Table 2, entry 5). Similarly, reaction of **16b** with **2b** at 0 °C provided **17b** in 76% yield at an 8:1 ratio (Table 2, entry 8). Unlike the reaction of **16b** with **2** that gave a high yield and a high diastereoselectivity, the reaction of **16c** (R = Bn) with **2b** afforded the desirable compound **17c** in 18% low yield. The N–H insertion product (30% yield) was the major product (Table 2, entry 10).

The stereochemistry of major and minor isomers was confirmed by NOE experiments (Figure 1). We were happy to find that the absolute configurations (*5S*, *6aR*, *11aS*) of the major isomer were in agreement with that found in aforesaid alkaloids. In the NOE experiments, the correlation between the α-proton of ester (H₁₃) and the aminal proton (H_{11a}) in **17b** was observed. Besides the correlation between the α-proton of ester (H₁₃) and the aminal proton (H_{11a}), the correlation between the aminal proton (H_{11a}) and the proton-H₅ of the oxazolidinone ring in **18b** was also observed.

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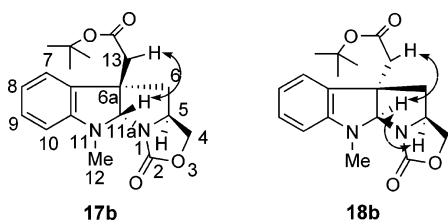


Figure 1. NOE experiments.

The effect of reaction temperature on the yield and diastereoselectivity was carefully studied to gain insight into the detailed mechanism of diastereoselectivity (Table 2). Both reactions of oxazolidinone **16b** with individual diazoesters **2a** and **2b** showed a narrow window of suitable temperature. For the reaction of **16b** with **2a**, the diastereoselectivity was greatly enhanced from a 1.4:1 ratio to a 17:1 ratio by lowering the temperature from 25 to -35 °C (Table 2, entries 2–5). For the reaction of **16b** with more bulky diazoester **2b**, the diastereoselectivity was slightly improved from a 7:1 to a 10:1 ratio by lowering the temperature from 25 to -5 °C (Table 2, entries 7–9). The temperature effect indicated that the cascade reaction proceeded under kinetic control. A tentative mechanism is suggested in Figure 2. Since the intermediates **19** and **20** were not detected during the reaction by TLC, it is reasonable to believe that the first step of cyclopropanation to form **19** and **20** should be the rate-controlling step in the cascade reaction, and that it proceeds much slower than the consecutive two steps of ring opening and cyclization. Because of the steric interaction between the oxazolidinone moiety and the indoline moiety in **20**, the formation of kinetically favorable transition state **19** should be easier than the transition state **20** that would lead to compound **18**. Presumably these effects are magnified at lower temperature.

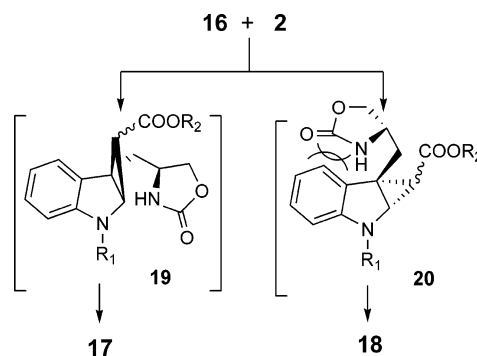


Figure 2. Proposed mechanism.

In summary, we have described a new and efficient synthetic method of chiral 3-substituted hexahydropyrroloindoline **17** in high yield by a one-pot cascade reaction from readily available L-tryptophan derivatives. Importantly, the synthesized framework **17** possesses the same absolute configurations as that appearing in natural products and necessary functional groups. Current methodology development has provided us an opportunity of synthetic approach to a variety of indole alkaloids such as physostigmine, bromoflustramide, mollenine, requefortine, ardeemin, amauromine, and aszonalenin.

Acknowledgment. The financial support of this work from NSFC (No. 20372048), Ministry of Education (NCET and RFDP), and Sichuan Province Government (No. 04ZQ026–011) is gratefully acknowledged.

Supporting Information Available: Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate Using Simple Bis(oxazoline) Ligands: Importance of Metal/Ligand Ratio

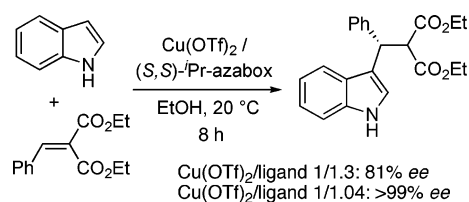
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ABSTRACT



Simple bis(oxazoline) ligands, especially azabis(oxazolines), can catalyze the copper-catalyzed addition of indoles to benzylidene malonates in up to >99% ee, provided that excess of chiral ligand is avoided. The paradigm followed in many asymmetric catalyses that an excess of chiral ligand with respect to the metal should improve enantioselectivity because a background reaction by free metal is suppressed, is not applicable here, which might call for revisiting some of the many copper(II)–bis(oxazoline)-catalyzed processes known.

Asymmetric Friedel–Crafts alkylations of indoles have been recently of great interest¹ due to the high relevance of indole derivatives as privileged structures in pharmaceutical drugs. Among them, the copper–bis(oxazoline)-catalyzed enantioselective 1,4-addition of indoles to α,β -unsaturated carbonyl compounds plays a prominent role, representing a facile, catalytic asymmetric process for this transformation.^{2–5} While in the pioneering work of Jørgensen and co-workers it was

demonstrated that copper(II) complexes with bis(oxazolines) **1a** can catalyze the asymmetric addition of indoles to α,β -unsaturated ketoesters with enantioselectivities of >99% ee,^{2a} using benzylidene malonates as substrates only proceeded with moderate selectivities (up to 69% ee) under the same reaction conditions.^{2b} Subsequently, Tang and co-workers reported some improvements of the latter reaction with bis(oxazoline) ligand **1b** (Table 1, entry 2)³ but most importantly demonstrated in a number of elegant studies that tris(oxazoline) ligands such as **3** were superior ligands for this process, giving the adduct **8a** with improved yields and selectivities up to 93% ee (Table 1, entry 4).⁴ A pentacoordinated copper(II) complex **A** was postulated as the decisive intermediate to account for the high selectivity. In summary, it was concluded from these studies that bis(oxazolines) are unsuitable ligands for the title reaction.

We report here that the ligand/copper ratio is crucial for the selectivity of the title reaction and that under optimized reaction conditions conjugate additions with benzylidene

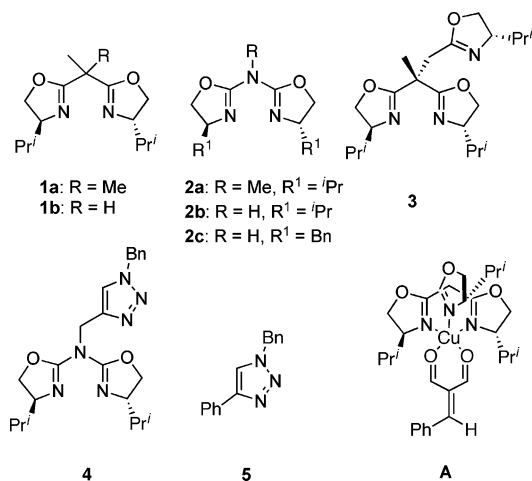
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(2) (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (b) Zhuang, W.; Hansen, T.; Jørgensen, K. A. *Chem. Commun.* **2001**, 347. (c) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739.

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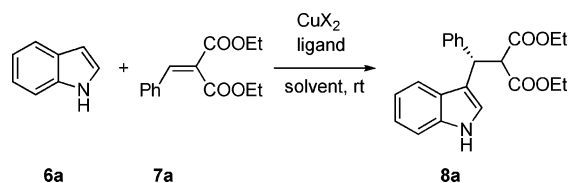
(5) (a) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154.



malonates can be performed with copper complexes of simple bis(oxazoline) and azabis(oxazoline) ligands in up to 99% ee.

Our investigation began with the finding that under standard conditions (5 mol % of $\text{Cu}(\text{ClO}_4)_2$, 5.5 mol % of ligand in an alcoholic solvent), azabis(oxazoline) **4**,⁶ having a triazole side arm, was able to catalyze under commonly employed conditions the transformation of indole **6a** to **8a** with significantly higher enantioselectivity than that of the

Table 1. Dependence of Enantioselectivity on Copper(II)/Metal Ratios in the Asymmetric 1,4-Addition to Benzylidene Malonates



entry	X in CuX_2	ligand	Cu/ligand		solvent	yield (%)	ee (%) ^a
			ratio	mol %			
1 ^b	OTf	1a	1/1.2	10/12	<i>i</i> -BuOH	85	79
2 ^c	OTf	1b	1/1.1	10/11	<i>i</i> -BuOH	99	82 ^d
3 ^c	OTf	1b	1/1.1	10/11	EtOH	94	76
4 ^b	OTf	3	1/1.2	10/12	<i>i</i> -BuOH	90	93
5	ClO_4	4	1/1.1	4.5/5.0	EtOH	93	95
6	ClO_4	2a	1/1.1	4.5/5.0	EtOH	88	70
7	ClO_4	2b	1/1.1	4.5/5.0	EtOH	85	66
8 ^e	ClO_4	2b	1/1.1	4.5/5.0	EtOH	92	81
9	ClO_4	2c	1/1.3	3.8/5.0	EtOH	90	87
10	ClO_4	2c	1/1.04	4.8/5.0	EtOH	96	95
11	OTf	2b	1/1.3	3.8/5.0	EtOH	98	81
12	OTf	2b	1/1.1	4.5/5.0	EtOH	93	85
13 ^f	OTf	2b	1/1.04	4.8/5.0	EtOH	97	>99
14	OTf	2b	1/1	5.0/5.0	EtOH	90	98
15	OTf	2b	1.1/1	5.5/5.0	EtOH	96	98
16	OTf	2b	1.3/1	6.5/5.0	EtOH	95	91
17	OTf	2b	7.5/0	7.5/0	EtOH	90	0
18	OTf	1a	1/1.04	4.8/5.0	EtOH	89	99

^a Determined by HPLC. ^b Taken from ref 4d. ^c Taken from ref 4c. ^d 75% yield, 93% ee at -25°C . ^e 5.5 mol % of triazole **5** was employed as an additive. ^f Obtained in three independent runs.

parent ligand **2b**⁷ or its corresponding N-methylated derivative **2a** (Table 1, entries 4–7), and it also exceeded the best values obtained with any tris(oxazoline) so far. This was unexpected since the rigid aza(bisoxazoline) framework should not allow tridentate coordination involving the triazole moiety. This hypothesis was confirmed by the X-ray structure of copper complex $\text{CuCl}_2\cdot\mathbf{4}$ (Figure 1), proving that the

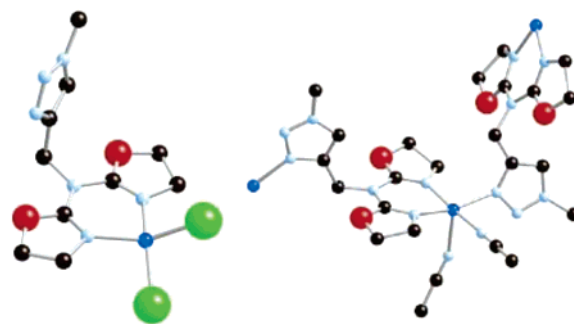


Figure 1. X-ray structures of $\text{CuCl}_2\cdot\mathbf{4}$ (left) and $[\text{Cu}(\text{ClO}_4)_2(\text{CH}_3\text{CN})_2\cdot\mathbf{4}]_n$ (right); *i*-Pr, Ph, and ClO_4 groups are omitted for clarity.

centralized sp^2 nitrogen turns the triazole side arm out of reach for coordination to the copper center. However, the X-ray structure of the complex obtained from **4** with $\text{Cu}(\text{ClO}_4)_2$ in acetonitrile revealed the ability of the triazole unit to coordinate copper in an intermolecular fashion via a second ligand molecule, resulting in a polymeric ligand structure bridged by copper atoms.

Consequently, we concluded that a bidentate bis(oxazoline) in combination with an external ligand such as a triazole should be sufficient to provide an effective chiral environment for the asymmetric addition of indoles to benzylidene malonates.

However, employing 1.1 equiv (based on copper) of triazole **5** as an additive in combination with ligand **2b**, while showing some benefit compared to ligand **2b** alone (entries 7 and 8), could not equalize the result obtained with ligand **4** (entry 5).

This observation suggested an alternative mechanism for the title reaction: While coordination by three nitrogen ligands to copper might represent a resting state of the catalyst, to reach the active species one of the nitrogen ligands has to dissociate off first. If bis(oxazoline) ligands are employed (Table 1, entries 1, 2, and 4–6), the excess ligand used might provide a third oxazoline moiety for coordination, and if subsequent dissociation of one of the chelating oxazoline moieties occurs to create a species such as **B**, selectivity should be low (Figure 2). Having weaker coordinating triazole moieties present would favor dissociation of that moiety, resulting in a species such as **C** that gives rise to high selectivity.

(6) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325.

(7) (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045. (b) Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166. (c) Geiger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249.

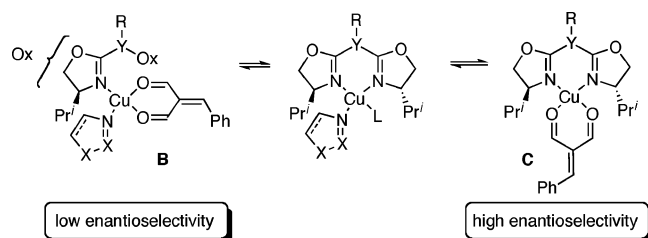


Figure 2. Mechanistic model for the asymmetric 1,4-addition to benzylidene malonates.

Following this line of argument, the superior results obtained with C_3 -symmetrical tris(oxazoline) **3** in comparison with bis(oxazolines) can also easily be understood since dissociation of any of the three oxazoline moieties should result in a species of type **C**.

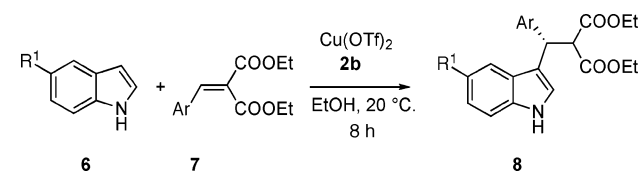
With ligand **4**, coordination of a third oxazoline moiety by the excess of ligand might be prevented due to steric effects, which is exhibited by the benzyl substituent on the triazole unit, again resulting in a species of type **C** giving rise to the high selectivity observed in contrast to employing ligand **2b** with an external triazole additive.

The rationale put forward above suggests that the ligand/copper ratio might have a decisive influence on the selectivity of the title reaction and, especially, that any *excess of ligand* might be detrimental. This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial in order to avoid background reactions by uncomplexed metal. Indeed, variation of the ratio of **2b**/copper showed a dramatic dependence on the enantioselectivity of **8a**, with the optimum being found when a ligand to copper ratio of 1.04/1 is used (Table 1, entries 11–16). Even employing an excess of copper (entries 15 and 16) still gives respectable but somewhat inferior selectivities, giving further credit to the hypothesis of an intermediate **C** as the decisive species for the catalytic process. A control experiment (entry 17) showed that the reaction proceeds well also in the absence of ligand, clearly demonstrating that the overall process is ligand accelerated. While we noticed a similar trend employing $\text{Cu}(\text{ClO}_4)_2$ as the copper source (entries 9 and 10), using $\text{Cu}(\text{OTf})_2$ gave better results and was therefore used for all subsequent reactions. Finally, although we generally obtain somewhat better results with the aza-(bisoxazoline) ligands, employing a copper/ligand ratio of 1/1.04 also gives very high selectivities with bis(oxazoline) **1a** (entry 18, cf. entries 1 and 3).

Applying this protocol for the reaction between other indoles and benzylidene malonates also gave good results, and with the exception of the strongly electron-deficient *p*-nitro derivative (entry 5), presumably an especially weak coordinating substrate for the copper–ligand complex, equaling or exceeding the selectivities obtained with tris(oxazolines)^{4a} (Table 2).

In conclusion, simple copper(II)–bis(oxazoline) complexes are excellent catalysts for the asymmetric addition of indoles

Table 2. Asymmetric Conjugate Addition between Indoles **6** and Benzylidene Malonates **7** at Room Temperature^a

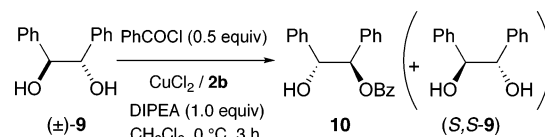


entry	Ar	R ¹	yield (%)	ee (%) ^b
1	Ph	H	97	99
2	<i>p</i> -Me-Ph	H	80	93
3	<i>p</i> -Cl-Ph	H	91	98
4	<i>o</i> -Br-Ph	H	89	85
5	<i>p</i> -NO ₂ -Ph	H	94	80
6	Ph	OMe	80	90

^a 4.8 mol % of $\text{Cu}(\text{OTf})_2$, 5.0 mol % of **2b**. ^b Determined by HPLC.

to benzylidene malonates provided that *excess of ligand with respect to copper metal employed is avoided*. This observation could also be significant for related asymmetric copper-

Table 3. Dependence of Enantioselectivity on Copper(II)/Metal Ratios in the Asymmetric Benzoylation of Diol (\pm)-**9**



entry	Cu/ligand ratio	Cu/ligand mol %	10 yield (%) ^a	10 ee (%) ^b
1	1.5/1.0	7.5/5.0	46	84
2	1.1/1.0	5.5/5.0	44	88
3	1.0/1.0	5.0/5.0	48	88
4	1.0/1.04	4.8/5.0	43	85
5	1.0/1.1	4.5/5.0	49	87
6	1.0/1.5	3.3/5.0	46	85

^a Isolated yield based on (\pm)-**9** (theoretical maximum yield 50%).

^b Determined by HPLC.

(II)– and other metal–bis(oxazoline) processes known⁸ that follow the paradigm that a slight excess of chiral ligands is advantageous to achieve higher asymmetric inductions. Especially in cases of reactions with substrates that only weakly coordinate to the metal complex, making binding of an oxazoline moiety from a second ligand a competitive process suggests that metal/ligand ratios must be carefully assessed. On the other hand, excess of bis(oxazoline) ligands in metal-catalyzed reactions is clearly not always detrimental to selectivity. For example, the copper(II)–azabis(oxazoline)-

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catalyzed⁶ asymmetric benzylation of 1,2-diols⁹ seems to be indifferent both to excess ligand as well as to excess metal (Table 3).

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kolleg NANOCAT (Elitenetzwerk Bayern), and the Fonds der Chemischen Industrie. Dr. M. Zabel, University of Regensburg, is acknowledged for carrying out the X-ray analyses.

Supporting Information Available: Experimental procedures, details on the X-ray structures, copies of ¹H and ¹³C spectra, and HPLC traces of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Copper(I)-Catalyzed Enantio- and Diastereoselective Tandem Reductive Aldol Reaction

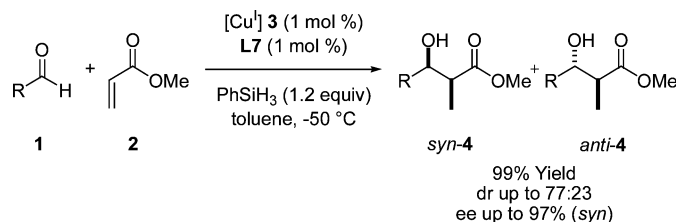
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ABSTRACT



An efficient method for the enantioselective tandem reductive aldol reaction of methyl acrylate with aldehydes is reported. By using a copper(I) precursor and a proper diphosphane ligand, high reactivities can be reached, with TOF up to 40 000 h⁻¹. Taniaphos-based ligands lead to enantioselectivities of up to 97% in the case of the major *syn* diastereoisomer.

The aldol reaction is a classical method for the creation of carbon–carbon bonds in organic synthesis.¹ Reductive aldol reaction of α,β -unsaturated esters with aldehydes promoted by catalytic amounts of various transition-metal complexes and a silane source is a powerful tool for stereocontrolled C–C bond formation.² By using this method, the preactivation of the nucleophile in an independent step is not required as the enolate (the activated form of the nucleophile) is generated in situ through the conjugated addition of a metal hydride onto a Michael acceptor. Previous works in this area has been described, including the obtention of good levels of diastereo- and enantioselectivity variants with rhodium or iridium metal complexes.³ We were interested in develop-

ing a more economic process and selected copper as the transition metal. To our knowledge, copper was only employed in intramolecular reductive aldol cyclization as the Stryker's reagent or as Cu(OAc)₂·H₂O.^{4–6} In a preliminary communication, we have recently reported a new catalytic method for the construction of stereogenic quaternary carbon

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(4) For intramolecular reductive aldol reactions with a stoichiometric amount of Stryker reagent, see: (a) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229. (b) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901. (c) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091. For intramolecular reductive aldol reactions with a catalytic amount of Stryker reagent, see: (d) Chiu, P.; Leung, S. K. *Chem. Commun.* **2004**, 2308. (e) Chiu, P. *Synthesis* **2004**, 2210. For intramolecular reductive aldol reactions catalyzed by Cu(OAc)₂·H₂O, see: (f) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225. (g) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

(1) For reviews on asymmetric aldol reactions, see: (a) Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357. (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Plattz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. III, Chapter 29.1, pp 997–1065. Mahrwald, R., Ed. *Modern Aldol Reactions*; Wiley-VCH: Weinheim, Germany, 2004. (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65.

(2) For original reports of catalytic reductive aldol reactions, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (c) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *37*, 5331. (d) Kiyooka, S.; Shimizu, A.; Torii, S. *Tetrahedron Lett.* **1998**, *39*, 237.

centers through a copper-catalyzed domino conjugated reduction/aldol reaction of methyl acrylate with various alkyl aryl ketones that gave high chemo-, diastereo-, and enantioselectivity.⁷ These results prompted us to investigate the use of this system for the construction of small propionate-type compounds.

In our initial experiment we used benzaldehyde **1a** (R = Ph) and methyl acrylate **2** (2.0 equiv), with a catalytic amount of [CuF(PPh₃)₃] \cdot 2MeOH (**3**),⁸ (*S*)-BINAP (**L1**), and a stoichiometric quantity of phenylsilane, at room temperature. In the presence of **3** and (*S*)-**L1** (0.01 mol %), a smooth reaction was almost complete within 15 min (94% conversion) affording the aldol adduct **4a** (*syn:anti*, 60:40) (ee_{syn} = 45%) and the benzyl alcohol **5a** in a ratio of 86:14. This catalytic system displays a very high activity and the TON was estimated to be 10.000 and the TOF to be 40 000 h⁻¹.

Cyclohexanecarboxaldehyde (**1b**, R = Cy) and **2** were also tested in the presence of **3** and (*S*)-**L1** (0.1 mol %) catalyst. The reaction was completed in 1 h at room temperature leading to **4b** (R = Cy) and **5b** (R = Cy) in a ratio of 89:11, a *syn:anti* diastereomeric ratio of 58:42, and an enantiomeric excess for the *syn* adduct of 30% (Table 1, entry 1).⁹

Table 1. Copper-Catalyzed Asymmetric Reductive Aldol Reaction with Various Ligands^a

entry	ligand	conversion (%) ^b		ee _{syn} (ee _{anti}) (%) ^c	
		4b:5b	<i>syn:anti</i>	4b:5b	<i>syn:anti</i>
1 ^{c-e}	L1	99	89:11	58:42	30
2 ^f	L2	99	88:12	70:30	60 (12)
3	L3	99	30:70	65:35	44
4	L4	99	67:33	64:36	57 (30)
5	L5	99	34:67	76:24	83
6	L6	75	2:98	52:48	38
7 ^c	L7	99	99:1	77:23	95 (74)
8 ^g	L7	99	97:3	77:23	94 (74)
9 ^f	L8	99	15:85	31:69	40 (30)
10	L9	39	6:94	63:37	61
11	L10	51	5:95	62:38	41

^a All reactions were carried out in solution (0.25 M) in THF at -78 °C under an oxygen-free argon atmosphere containing **1b** (1.0 equiv), **2** (1.2 equiv), **3** (1 mol %), ligand (1 mol %), and PhSiH₃ (1.4 equiv) unless otherwise stated. ^b Determined by chiral GC analysis CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). ^c **3** (0.1 mol %), ligand (0.1 mol %). ^d **1b** (0.8 equiv), **2** (1.0 equiv), **3** (1.25 mol %), ligand (1.25 mol %), PhSiH₃ (1.2 equiv). ^e At room temperature. ^f At 0 °C. ^g In toluene.

Despite the high activity of this catalytic system and the rather good chemoselectivity attained, **4a,b** (R = Ph or Cy) was obtained only with moderate diastereomeric and enantiomeric excesses. To optimize these results, several parameters were modified. Some chiral ligands were initially screened in THF at lower temperature (-78 °C). Various

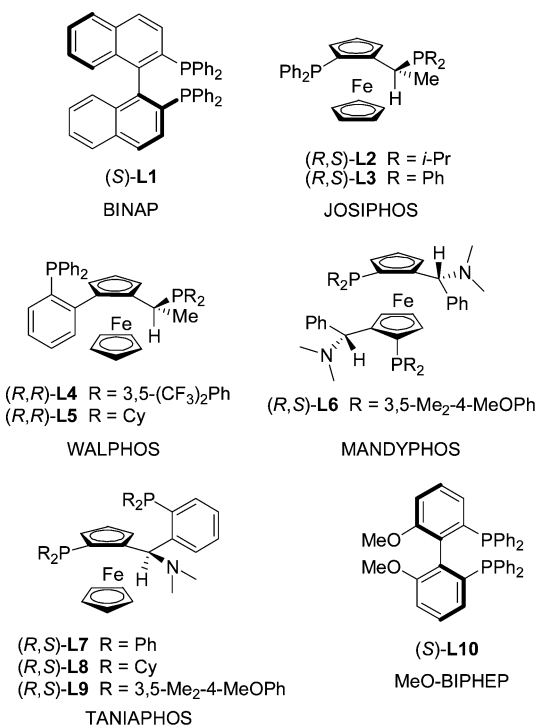


Figure 1. Chiral diphosphane ligands evaluated in asymmetric reductive aldol reaction.

families of chiral diphosphane ligands **L2–L10** (Figure 1) were employed and some of the most pertinent results are summarized in Table 1 (entries 2–11), with cyclohexanecarboxaldehyde (**4b**) as the substrate.¹⁰ The reactions were almost complete in less than 2 h, regardless of the ligand's structure (except entries 6, 10, and 11). However, the ratio between **4b** and **5b** fluctuates and depends upon the structure

(5) For intramolecular reductive aldol cyclizations catalyzed by Wilkinson's complex, see: (a) Emiabata-Smith, D.; McKillop, A.; Mills, C.; Motherwell, W. B.; Whitehead, A. J. *Synlett* **2001**, 8, 1302. (b) Freiria, M.; Whitehead, A. J.; Tocher, D. A.; Motherwell, W. B. *Tetrahedron* **2004**, 60, 2673.

(6) Alternatively, molecular hydrogen may be used as the reducing agent for the reductive aldol cyclization catalyzed by rhodium and cobalt complexes, see: (a) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, 123, 5112. (b) Huddleston, R. R.; Krische, M. J. *Org. Lett.* **2003**, 5, 1143. (c) Jang, H. Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, 37, 653. (d) Jang, H. Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953.

(7) (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, 45, 1292. After our submission, Shibasaki reported a similar catalytic system for the reductive aldol reaction: (b) Zhao, D. B.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, 47, 1403.

(8) The complex was prepared according to a literature procedure, see: Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, 52, 153. The amount of methanol molecules was determined by single-crystal X-ray crystallographic analysis of the complex (unpublished results).

(9) *Syn* and *anti* diastereoisomers were identified by comparison of chemical shifts obtained by ¹H NMR with those reported by Morcken et al.^{3a-e} and Nishiyama et al.^{3h} Conversion, chemo-, diastereo-, and enantioselectivities were determined by chiral GC. Analytical gas chromatography was performed on a ThermoFinnigan Trace GC, using a CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). The ratios are based upon crude integrations which correspond to the corrected integrations by calibration.

(10) For example, monodentate Feringa phosphonite, bidentate Reetz phosphites, and tetradentate Trost ligands gave also good activities but low diastereo- and enantioselectivities.

of the ligands. In some cases, the chemoselectivity could almost be completely shifted in favor of the reduction product **5b** (Table 1, entries 6, 9, 10, and 11). Promising results were observed in the case of ligands JOSIPHOS **L2**, WALPHOS **L4**, and **L5**. Good enantioselectivities were reached in the case of the *syn* isomer (Table 1, entries 2, 4, and 5). We subsequently tested TANIAPHOS ligands **L7–L9**, which contain a 1,5-diphosphane unit and hence are capable of forming an eight-membered chelate ring with the metal. To our delight, **L7** provided a remarkable improvement in the chemoselectivity in favor of **4b** (99:1), with a diastereoselectivity (dr 77:23) (Table 1, entries 7 and 8) similar to that obtained with the **L2** or **L4** ligands, in favor of the *syn* adduct (Table 1, entries 2 and 4). However, the enantiodifferentiation was drastically enhanced for both isomers of **4b**. Under these conditions, the reaction with **L7** furnished adduct **4b** with 95% ee and 74% ee for the *syn* and *anti* isomers, respectively (Table 1, entry 7). The catalyst loading can be decreased to 0.1 mol % without any variation in chemo-, diastereo-, and enantioselectivities (Table 1, entries 1 and 7). Interestingly, TANIAPHOS **L8** and **L9** showed poor results in the reductive aldol reaction compared to **L7** (Table 1, entries 9 and 10).

Next, we studied the scope of the copper-catalyzed asymmetric reductive aldol reaction with respect to the aldehyde substrates and the TANIAPHOS chiral ligand **L7**, under optimal conditions. A variety of aliphatic, aromatic, or heteroaromatic aldehydes were tested at $-78\text{ }^{\circ}\text{C}$ in THF. However, the low solubility of aromatic substrates at low temperature in THF or toluene forced us to select a compromise in which in toluene, at $-50\text{ }^{\circ}\text{C}$, provided the best results.¹¹ Remarkably, the selectivity of the domino process did not change when THF was replaced by toluene, and we observed that all substrates participate successfully in the reaction (conversion >99%). The chemoselectivity remains excellent (generally >95:5) with good enantioselectivities but moderate diastereoselectivities (Table 2). The isolated yields for the corresponding adducts after chromatographic purification were all in the range of 74–99%. For acyclic aliphatic aldehydes, good chemoselectivities and moderate diastereoselectivities were observed (entries 1 and 2) and some enantioselectivity was detected in the case of isobutyraldehyde ($ee_{syn} = 73\%$) (entry 1).

Nevertheless, the domino process was more efficient when aromatic and heteroaromatic aldehydes were employed. For the range of substrates studied, the chemoselectivity was

(11) General procedure for catalytic reductive aldol reaction: A 10 mL flame-dried round-bottomed flask, equipped with a magnetic stirrer, was charged with $\text{CuF}(\text{PPh}_3)_2 \cdot 2\text{MeOH}$ (9.0 mg, 0.01 mmol), ligand (0.01 mmol), and toluene (4.8 mL). The catalyst solution was stirred for 30 min at room temperature and phenylsilane (180 μL , 1.40 mmol) was added at the same temperature. After the solution was cooled at $-50\text{ }^{\circ}\text{C}$, methyl acrylate (110 μL , 1.20 mmol) and the corresponding aldehyde (1.00 mmol) were simultaneously added to the solution. The mixture was stirred for 1 h at $-50\text{ }^{\circ}\text{C}$ under argon. Conversion, dr and ee were followed by gas chromatography (aliquots were hydrolyzed by 1 mL of aqueous NH_4F solution and filtered through a plug of silica). The reaction mixture was quenched by adding aqueous NH_4F solution (5 mL). The aqueous layer was extracted by diethyl ether (3 \times 5 mL). Then, the combined organic layers were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography to yield the corresponding adduct.

Table 2. Asymmetric Copper-Catalyzed Reductive Aldol Reaction between **2** and Various Aldehydes **1** in the Presence of (*R,S*)-**L7** under the Optimal Conditions^a

entry	R	conversion (%) ^b		ee_{syn} (ee_{anti}) (%) ^c	
		4:5	<i>syn:anti</i>		
1	<i>i</i> -Pr	99	100:0	64:36	73 (26)
2	<i>t</i> -Bu	99	77:23	76:24	0 (0)
3	Cy	99	100:0	57:43	86 (70)
4	Cy ^d	99	99:1	77:23	96 (74)
5	Cy ^e	99	100:0	88:12	97 (30)
6	C_6H_5	99	95:5	41:58	nd (72)
7	<i>p</i> - FC_6H_4	99	97:3	44:56	86 (76)
8	<i>p</i> - $\text{CF}_3\text{C}_6\text{H}_4$	99	74:26	47:53	84 (65)
9	<i>p</i> - ClC_6H_4	99	95:5	44:56	85 (69)
10	<i>p</i> - MeOC_6H_4	99	95:5	60:40	68 (72)
11	<i>o</i> - MeOC_6H_4	99	95:5	41:59	58 (78)
12	2-thienyl ^{d,f}	99	95:5	67:33	83 (nd)
13	3-thienyl	99	99:1	51:49	86 (76)
14	2-pyridyl ^d	94	82:18	67:33	34 (44)

^a All reactions were carried out in toluene (0.25 M) at $-50\text{ }^{\circ}\text{C}$ under an oxygen-free argon atmosphere containing **1** (1.0 equiv), **2** (1.2 equiv), **3** (1 mol %), **L7** (1 mol %), and PhSiH_3 (1.4 equiv) unless otherwise stated.

^b Determined by chiral GC analysis CHIRALSIL-DEX CB (25 m, 0.25 mm, 25 μm). ^c Configuration determined by comparison with known products. ^d At $-78\text{ }^{\circ}\text{C}$. ^e Ph_2SiH_2 (1.4 equiv) instead of PhSiH_3 . ^f In THF.

good to excellent but the diastereoselectivity remained moderate, favoring either the *syn* or the *anti* isomers (Table 2, entries 6 to 14). In all cases, good to excellent enantiomeric excesses were obtained (up to 86% for the *syn* isomer) at $-50\text{ }^{\circ}\text{C}$. As a general trend, the introduction of a halogen substituent at the *para* position (entries 7 to 9) did not change the selectivity, whereas the replacement of an electron-withdrawing group, at the *para* position of benzaldehyde, by an electron-donating group increased the diastereoselectivity in favor of the *syn* isomer. Unfortunately, the enantiomeric excess on the *syn* isomer was slightly decreased (Table 2, entry 10).

Heteroaromatic aldehydes, such as 2- and 3-thiophene-substituted aldehydes, also took part efficiently in the domino sequence to give the *syn-4* adducts with rather good enantioselectivities (Table 2, entries 12 and 13).

We have also investigated the dependence of the structure of the silane on the domino process. Various silanes were tested, such as $(\text{Me}_3\text{SiO})_2\text{MeSiH}$, Me_2EtOSiH , $(\text{Me}_2\text{SiH})_2\text{O}$, or PMHS, in the reductive asymmetric aldol reaction process, with carboxylaldehyde as the electrophile. Unfortunately, only Ph_2SiH_2 gave excellent results as the diastereomeric ratio and the enantiomeric excesses were both improved at $-50\text{ }^{\circ}\text{C}$ in toluene (*syn:anti* 88:12, $ee_{syn} = 97\%$) (Table 2, entries 3 and 4 versus 5). Alas, Ph_2SiH_2 did not lead to significantly improved selectivities with the other aldehydes used.

In summary, we have developed a new catalytic asymmetric system for the reductive/aldol reaction sequence between methyl acrylate and various aldehydes. The process, catalyzed by a chiral diphosphane modified copper(I) fluoride complex, in the presence of phenylsilane or diphenylsilane, is highly chemoselective but gives moderate diastereoselectivity. However, good to excellent enantioselectivities were obtained for a wide range of cyclic aliphatic, aromatic, and heteroaromatic aldehydes when the TANIAPHOS ligand **L7** was employed. This observation clearly reveals that the key parameter in this reaction strongly depends on the choice of the ligand.¹²

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Unprecedented Effects of Additives and Ligand-to-Metal Ratio on the Enantiofacial Selection of Copper-Catalyzed Alkynylation of α -Imino Ester with Arylacetylenes

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Abstract: The first catalytic asymmetric addition of arylacetylenes to α -imino esters was carried out using chiral copper(I) complexes as catalysts under mild reaction conditions, providing the corresponding alkynylation products in good yields with 67–74% *ee* values. Profound effects of the ligand-to-metal ratio and additives on the stereofacial selection were observed. Both enantiomers of a given product can be obtained with almost identical enantiomeric excess using the same chiral ligand by adjusting the ligand-to-metal ratio.

Keywords: asymmetric alkynylation; asymmetric catalysis; copper; enantioselectivity; α -imino ester; ligand-to-metal ratio

Optically active non-proteinogenic α -amino acids are important compounds in biological systems and chiral building blocks in drug syntheses.^[1–6] A special class of these compounds are chiral β,γ -alkynyl- α -amino acid derivatives.^[7] It is recognized that compounds containing carbon/carbon triple bonds serve to deactivate a variety of enzymes.^[8] However, the synthesis of enantiomerically enriched β,γ -alkynyl- α -amino acid derivatives is a challenging undertaking.

Metal-catalyzed addition of terminal alkynes to imines represents one of the most convenient methods for the synthesis of propargylamines.^[9] This reaction was extended to α -imino esters and an efficient synthesis of β,γ -alkynyl- α -amino acid derivatives was developed by the direct addition of phenylacetylene and alkylacetylenes to an α -imino ester in the presence of silver(I) salts.^[10] Based on this method, we realized the first catalytic asymmetric synthesis of aliphatic alkynyl- α -amino acid derivatives by using cop-

per(I) complexes with 48–91% enantiomeric excesses.^[11] From a synthetic standpoint, an efficient and flexible approach to enantiomerically pure aromatic alkynyl- α -amino acid derivatives is highly desirable. In this paper, we report the first enantioselective addition of arylacetylenes to an α -imino ester, and reveal unprecedented effects of the ligand-to-metal ratio and additives on the enantiofacial selection of the Cu-catalyzed alkynylation of an α -imino ester with arylacetylenes.

The experiments were carried out under similar conditions to those used in our previous study of Cu-catalyzed addition of aliphatic alkynes to the α -imino ester.^[11] The reaction of phenylacetylene **2a** and α -imino ester **1** was performed in dichloromethane (DCM) at -10°C using 10 mol% CuOTf \cdot 0.5C₆H₆ as a precatalyst, Pybox **10** (Figure 1) as a chiral ligand and 0.1 equivalent of PMP-NH₂ as additive. The desired product **3a** was obtained with moderate yield (51%) and low enantiomeric excess (41% *ee*) after 48 h. Although the cause of this phenomenon was not immediately clear, this result indicated the difference in reactivity between aliphatic and aromatic alkynes in the Cu-catalyzed alkynylation of the α -imino ester, and that new reaction conditions must be established for arylacetylenes. To our delight, further experiments indicated that, in the absence of an additive, the yield and enantiomeric excess of the addition product **3a** increased significantly to 64% and 61%, respectively, at -10°C after 48 h. After further optimization, we obtained the product **3a** in 75% yield and 60% *ee* at room temperature after 24 h.

These interesting results led us to examine the effect of a variety of chiral ligands (Figure 1) in the Cu-catalyzed asymmetric addition of phenylacetylene **2a** to the α -imino ester **1**. Similar to the previously reported results in the enantioselective addition of aliphatic alkynes to the α -imino ester,^[11] BINAP was

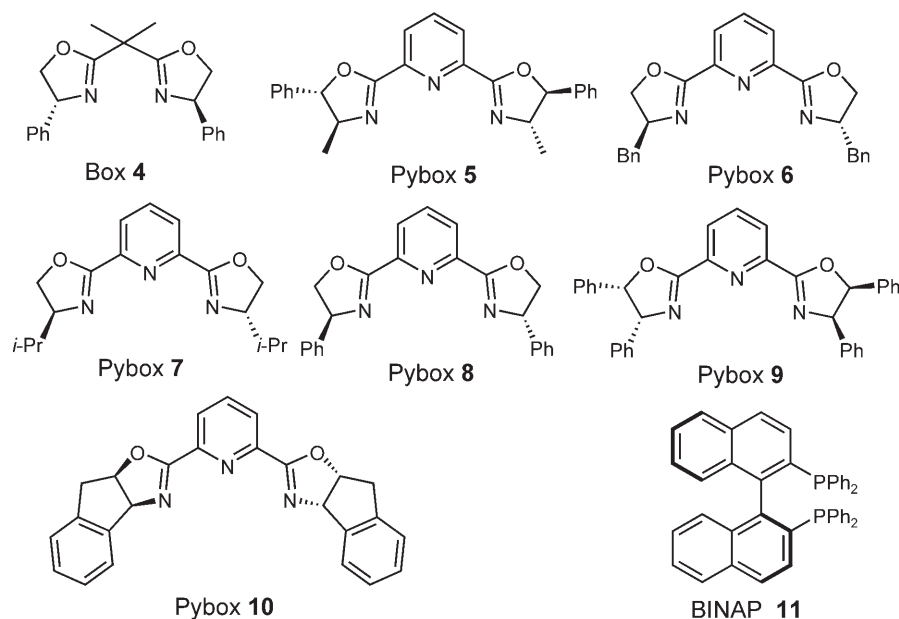
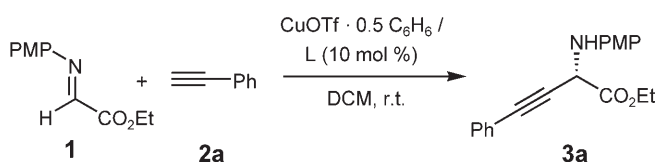


Figure 1. Chiral ligands tested in the addition of aromatic alkynes to an α -imino ester.

less effective in this reaction (Table 1, entry 8). Given that chiral copper-bis(oxazoline) (box) complexes have been successfully applied in numerous enantioselective addition reactions,^[12–14] a variety of chiral bis(oxazolonyl) ligands were tested. Among the chiral ligands that we have investigated, the commercially available chiral ligand Pybox **8** furnished the target product **3a** with the best result (80% yield, 63% *ee*)

Table 1. Effects of different chiral ligands on reactivity and enantioselectivity.^[a]



Entry	Ligand	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	4	68	<5
2	5	65	<5
3	6	trace	not determined
4	7	66	49
5	8	80	63
6	9	65	61
7	10	75	60
8	11	54	<5

^[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol % catalyst at room temperature.

^[b] Isolated yield.

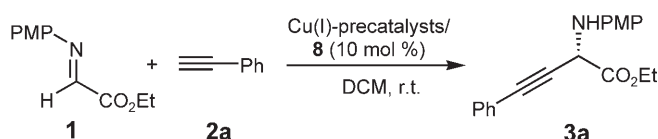
^[c] Determined by chiral HPLC using a Chiralpak AD-H column.

(entry 5). Pybox **10**, which was the most effective ligand used in the enantioselective addition of aliphatic alkynes to the α -imino ester,^[11] gave slightly lower yield (75% yield) and enantiomeric excess (60% *ee*) (entry 7).

Other Cu(I) pre-catalysts in combination with ligand **8** were also investigated in this reaction (Table 2). $\text{CuPF}_6 \cdot 4\text{MeCN}$ gave relatively lower yield (62% yield) and enantiomeric excess (54% *ee*) under the same conditions (entry 1), and CuBr and CuCl did not show any catalytic activity (entries 2 and 3).

We then studied the effect of ligand-to-metal ratio in this $\text{CuOTf} \cdot 0.5\text{C}_6\text{H}_6$ -catalyzed reaction (Table 3).

Table 2. Effects of different Cu(I) pre-catalysts on reactivity and enantioselectivity.^[a]

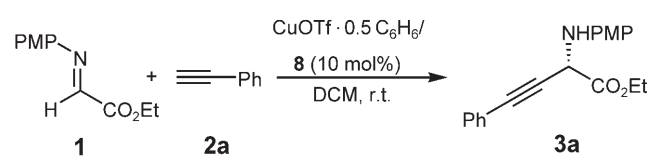


Entry	Cu(I) pre-catalyst	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	$\text{CuPF}_6 \cdot 4\text{MeCN}$	62	54
2	CuBr	0	
3	CuCl	0	

^[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol % catalyst at room temperature.

^[b] Isolated yield.

^[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Table 3. Effects of different ratio of CuOTf·0.5C₆H₆ to chiral ligand **8** on reactivity and enantioselectivity.^[a]

Entry	Ratio of 8 to CuOTf·0.5C ₆ H ₆	Yield [%] ^[b]	ee [%] ^[c]
1	1:1	80	63 ^[d]
2	1.1:1	74	60 ^[d]
3	1.2:1	64	23 ^[e]
4	1.25:1	60	2 ^[e]
5	1.3:1	57	-36 ^[e]
6	1.5:1	54	-62 ^[f]
7	2:1	34	-63 ^[f]
8	1:1.2	70	50 ^[d]
9	1:1	71	-23 ^[g]
10	1.5:1	60	-70 ^[h]

^[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol% catalyst at room temperature.

^[b] Isolated yield.

^[c] Determined by chiral HPLC using a Chiralpak AD-H column.

^[d] 24 h.

^[e] 36 h.

^[f] 6 days.

^[g] 24 h, 4 Å MS added.

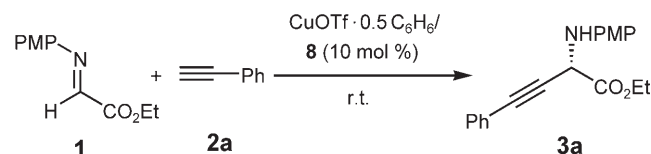
^[h] 6 days, 4 Å MS added.

When the ratio of Pybox **8** to CuOTf·0.5C₆H₆ was changed from 1:1 to 1.1:1, a slightly lower *ee* was obtained (entry 2). The observation that a small excess of ligand is detrimental to enantioselectivity is in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial to suppress the background reaction catalyzed by uncomplexed metal. When the ratio of Pybox **8** to CuOTf·0.5C₆H₆ was changed from 1:1 to 1.25:1, the *ee* value dramatically decreased to almost 0% (entry 4). This observation indicated that the ligand-to-metal ratio might have a decisive influence on the enantioselectivity of the reaction. Further increase of the ratio of Pybox **8** to CuOTf·0.5C₆H₆ to 1.5:1 dramatically switched the product enantioselectivity to the opposite sense. The product **3a** was obtained with almost identical *ee* (62% *ee*) but with opposite enantiofacial selection (entry 6). This is surprising yet most interesting since both enantiomers of a given product with almost the same enantiomeric excess can be prepared with the same chiral ligand by simply adjusting the ligand-to-metal ratio. Although usually both enantiomers of a chiral compound can be prepared by using the opposite enantiomers of a chiral ligand, sometimes one of the enantiomers of a chiral ligand may not be readily

available. Our finding offers an interesting alternative to provide both enantiomers of a chiral compound.

Interestingly, the addition of 4 Å molecular sieve to the reaction system also resulted in the switch of the enantioselectivity of product **3a** (entry 9). When 4 Å MS was combined with CuOTf·0.5C₆H₆/Pybox **8** (1:1.5), -70% *ee* was obtained (entry 10). The switch of the stereofacial selection might be due to a different mode of coordination. However, further studies certainly are needed to elucidate this interesting phenomenon.

A profound solvent effect on the yield and enantioselectivity of the reaction was also observed (Table 4). For example, when toluene was used as solvent, only 30% *ee* was obtained (entry 1). DCM was the best choice of solvent for reactivity and enantioselectivity (entry 5).

Table 4. Effects of the choice and concentration of solvent on the reactivity and enantioselectivity.^[a]

Entry	Solvent	Solvent volume [mL]	Yield [%] ^[b]	ee [%] ^[c]
1	toluene	1.5	81	30
2	THF	1.5	40	44
3	DCM	1.5	80	63
4	DCM	1.2	78	66
5	DCM	1.0	80	70
6	DCM	0.8	76	69
7	DCM	0.6	65	57

^[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** with 10 mol% catalyst at room temperature.


^[b] Isolated yield.

^[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Under the optimized conditions, the scope of nucleophiles in the reaction system was examined, and the results are summarized in Table 5. The electronic property of the substituents on the aromatic ring did not show significant effects on the reactivity and stereoselectivity of Cu-catalyzed alkylation of the α -imino ester. The arylacetylenes bearing either an electron-donating group or an electron-withdrawing group reacted smoothly with the α -imino ester, providing the corresponding alkylation products with good yields and 67–74% *ee* values.

To determine the absolute configuration, product **3a** was converted to 2-amino-4-phenylbutyric ethyl ester hydrochloride **12** (Scheme 1). The (*S*) configura-

Table 5. Cu-catalyzed addition aromatic alkynes to α -imino ester **1**.^[a]



Entry	2 (Ar)	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	80 (3a)	70
2	Ph	74 (3a)	73 ^[d]
3	4-MeO-C ₆ H ₄	65 (3b)	67
4	4-Me-C ₆ H ₄	80 (3c)	74 ^[e]
5	4-Br-C ₆ H ₄	86 (3d)	69 ^[f]

^[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of aromatic alkynes **2** in 1.0 mL DCM with 10 mol % catalyst.

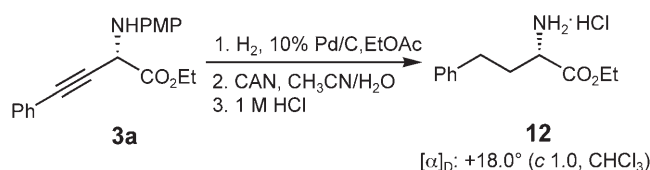
^[b] Isolated yield.

^[c] Determined by chiral HPLC using a Chiralpak AD-H column except entry 4.

^[d] 0°C, 48 h.

^[e] Determined by chiral HPLC using a Chiralcel OD-H column.

^[f] 0°C, 24 h.



Scheme 1. Determination of the absolute configuration of **3a**.

tion was established by comparison of the optical rotation of **12** with the previously reported value of this compound.^[15]

In conclusion, we have carried out the first catalytic asymmetric alkylation of an α -imino ester with aryl-alkynes using a commercially available chiral ligand **8**. There are several features to this enantioselective alkylation: (1) the experimental procedure is convenient and simple, and the use of additives can be avoided; (2) two enantiomers of the desired product can be prepared in almost the same enantiomeric excess with the same chiral ligand simply by adjusting the ligand-to-metal ratio. The rich chemistry of the alkylation functionality and the aromatic functionality makes the present method a powerful and versatile approach to a wide range of optically active α -amino acid derivatives. A study aiming at elucidating the reaction mechanism and improving the enantioselectivity is in progress.

Experimental Section

Typical Procedure for Catalytic Asymmetric Alkylation of α -Imino Ester **1**

Pybox **8** (9.2 mg, 0.025 mmol) and CuOTf·0.5 C₆H₆ (6.3 mg, 0.025 mmol) were added to a dried 5-mL reaction flask containing a magnetic stirring bar. CH₂Cl₂ (0.5 mL) was added, and the mixture was stirred at room temperature for 1 h. Then α -imino ester **1** (52 mg, 0.25 mmol) in CH₂Cl₂ (0.5 mL) and alkyne (0.5 mmol) were sequentially added under vigorous stirring. The resulting solution was stirred at room temperature until TLC monitored the completion of the reaction. The mixture was then passed through a short plug of silica gel that was subsequently washed with ether. The combined solution was concentrated under vacuum. The purification of the residue by flash silica gel column chromatography yielded the corresponding alkylation product. The enantiomeric excess of the product was determined by chiral HPLC analysis.

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Simple and Efficient Heterogeneous Copper Catalysts for Enantioselective C–H Carbene Insertion

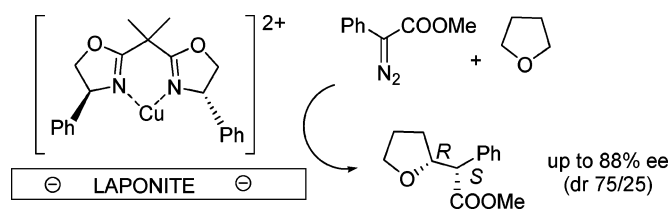
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ABSTRACT



Immobilized box–Cu complexes are able to efficiently catalyze the insertion of a carbene, from methyl phenyldiazoacetate, into C–H bonds of THF, with high enantioselectivity (up to 88% ee). The immobilization not only allows recovery and reuse of the enantioselective catalyst but also provides an improvement in the selectivities from the values obtained in solution, probably due to a confinement effect of the bidimensional support.

Functionalization of C–H bonds is currently an important field of research in chemistry. Whereas catalytic oxidative addition is still challenging, the metal-catalyzed insertion of carbenes, generated from diazo compounds, is a well-established alternative method to functionalize C–H bonds.¹ Rhodium catalysts have proven to be the most efficient for the asymmetric version of this reaction, mainly the intramolecular variant,² and this approach has been extended in recent years to intermolecular reactions.³ In contrast, copper catalysts have hardly been used for this type of reaction. Only in the past few years did Pérez and co-workers show that trispyrazolylborate complexes of copper, silver, and gold are active and selective in the intermolecular insertion of carbenes.⁴ Regarding the asymmetric insertion reactions, copper catalysts have only been successful in the intramolecular version.^{5,6} In this communication, we demonstrate

that for the first time the cheap and easily accessible bis(oxazoline)–copper complexes can act as efficient catalysts for this type of reaction provided they are immobilized onto a bidimensional clay by simple cationic exchange.

Four different ligand families were chosen for this study (Figure 1): the C₂-symmetric bis(oxazoline)⁷ (box, **1**) and azabis(oxazoline)⁸ (azabox, **2**) ligands and the nonsymmetric quinoxalineoxazoline⁹ (quox, **3**) system. All of these ligands are known to form copper complexes that efficiently catalyze

(4) Examples of carbene insertions in aliphatic C–H bonds: (a) Urbano, J.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. *J. Organometallics* **2005**, *24*, 1528–1532. (b) Caballero, A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. *J. Am. Chem. Soc.* **2003**, *125*, 1446–1447. (c) Caballero, A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. *Organometallics* **2003**, *22*, 4145–4150. For other carbene insertions, see: (d) Díaz-Requejo, M. M.; Pérez, P. *J. Organomet. Chem.* **2005**, *690*, 5441–5450 and references cited therein.

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(6) Recently, an enantioselective copper-catalyzed intramolecular O–H insertion has been described: Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595.

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(2) Davies, H. M. L.; Beckwith, R. E. *J. Chem. Rev.* **2003**, *103*, 2861–2903.
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(b) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176–4187.

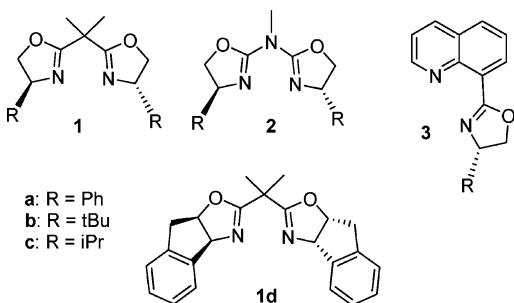
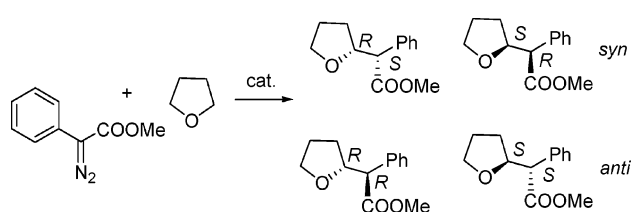


Figure 1. Ligands used for enantioselective C–H carbene insertion.

the cyclopropanation of alkenes with diazo compounds and therefore were good candidates for the insertion reaction.

Different copper salts were tested in the homogeneous phase: Cu(OTf)₂, CuBr₂, Cu(OAc)₂, CuCl, and CuSbF₆ (prepared from CuCl and AgSbF₆). Copper triflate was clearly better than the chloride, bromide, and acetate, as also occurs in cyclopropanation reactions,¹⁰ and CuSbF₆ did not show any significant improvement. Cu(OTf)₂ was therefore used due to its ease of handling. Catalysts were tested in the insertion of methyl phenyldiazoacetate in THF¹¹ under reflux (Scheme 1), and the results of the homogeneous reactions are gathered in Table 1.

Scheme 1. Reaction between Methyl Phenyldiazoacetate and THF



As can be seen, all the catalysts, including copper triflate itself, are active in this reaction, with yields in the range 40–50%. However, azabox ligands (**2**) are clearly superior, even leading to 85% in the case of the phenyl-substituted

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Table 1. Results of the Reactions between Methyl Phenyldiazoacetate and THF Catalyzed by Homogeneous Copper Complexes^a

ligand	conversion ^b (%)	syn/anti	% ee syn	% ee anti
–	41	75:25	–	–
1a	48	64:36	59	40
1b	49	71:29	2	6
1d	48	71:29	14	27
2a	85	64:36	59	55
2a^c	39	60:40	57	40
2a^d	20	77:23	2	4
2b	54	74:26	1	12
2c	74	56:44	64	48
3a	44	72:28	6	6

^a Reaction conditions: 2% Cu(OTf)₂, 2.2% ligand, THF as solvent, slow addition (2 h) of diazo compound, reflux. Conversion and diastereoselectivity were determined by gas chromatography. Enantioselectivities were determined by HPLC (Chiralcel OD-H). The major syn isomer has the absolute configuration 2*R*, α *S*, from the sign of the optical rotation (ref 11). ^b Conversion to insertion products. As total conversion of the diazo compound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. ^c Reaction carried out at room temperature with 4% catalyst. ^d Reaction carried out in hexane under reflux with 2 equiv of THF.

ligand (**2a**). Regarding enantioselectivity, only symmetrical ligands are efficient and both box and azabox ligands with the same substituents lead to a similar enantiomeric excess. Phenyl or isopropyl substituents show higher enantioselectivity, around 60% ee, than *tert*-butyl—a situation in contrast with the behavior of the same ligands in the related cyclopropanation reaction. However, one drawback of these systems is the lower diastereoselectivity, which is associated with the higher enantioselectivity. These results are slightly worse than those obtained with Rh₂(*S*-DOSP)₄ under the same conditions (2:1 diastereomeric ratio, 72% ee syn),¹¹ and we tried to improve the enantioselectivity of ligand **2a** by using the same strategies, i.e., lowering the temperature or using hexane as solvent. At room temperature, the yield was lower and the enantioselectivity was not improved. The use of hexane was very detrimental, in terms of both yield and enantioselectivity, probably due to the low solubility of the **2a**–Cu complex. The stereochemical course of the insertion of carbene with copper catalysts cannot be outlined, as the reaction mechanism is still poorly understood.

There are very few examples in the literature concerning the use of heterogeneous catalysts for the enantioselective insertion of carbenes into C–H bonds.¹² The best homogeneous catalysts in our tests were selected for immobilization onto laponite clay by cationic exchange in methanol.¹³ The heterogeneous catalysts were used under the same conditions as the homogeneous ones. The reactions were truly heterogeneous, as shown by filtration experiments, and leaching of copper was not detected by ICP analysis.

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Azabox ligands form very stable complexes, which allows an efficient immobilization by electrostatic interactions.^{13a} In this case, ligands **2a–c** lead to results very similar to those in solution, with the important practical advantage of being fully recoverable at least twice. Surprisingly, the immobilization of **3a** produces a significant increase in the enantioselectivity, from virtually zero to values in the region of 40% ee (Table 2). This result represents a new example of a

Table 2. Results of the Reaction between Methyl Phenyl diazoacetate and THF Catalyzed by Laponite-Supported Copper Complexes^a

ligand	run	conversion ^b (%)	syn/anti	% ee syn	% ee anti
–	1	21	52:48	–	–
1a	1	66	75:25	84	39
	2	71	77:23	83	40
	3	72	75:25	82	39
	4	65	72:28	81	40
	5	37	54:46	28	24
1a^c	1	59	78:22	88	46
	2	40	74:26	85	46
2a	1	60	74:26	58	51
	2	55	74:26	57	51
	3	61	73:27	56	54
2a^c	1	43	71:29	71	56
	2	42	71:29	66	53
	3	44	71:29	66	56
2b	1	27	51:49	2	16
2c	1	50	59:41	62	59
	2	56	58:42	61	59
	3	62	56:44	58	56
3a	1	31	60:40	30	0
	2	44	60:40	41	2
3a^c	1	35	62:38	44	9
	2	30	64:36	45	8

^a Reaction conditions: 2% catalyst, THF as solvent, slow addition (2 h) of diazo compound, reflux. Conversion and diastereoselectivity were determined by gas chromatography. Enantioselectivities were determined by HPLC (Chiralcel OD-H). The major syn isomer has the absolute configuration 2*R*, α *S*, from the sign of the optical rotation (ref 11). ^b Conversion to insertion products. As total conversion of the diazo compound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. ^c Reaction carried out in hexane under reflux with 2 equiv of THF.

surface effect, which has already been observed in cyclopropanation reactions.^{14,15}

The best results were obtained with box **1a**. The immobilized catalyst gave rise to 84% ee with a diastereomeric ratio of 75:25, a significant improvement from the homo-

geneous results (61% ee and 64:36 dr). Moreover, this catalyst is also recoverable and can be used three more times with the same results, thus demonstrating the stability of the **1a**–Cu complex.¹³ In fact, after four runs, each catalytic center of the **1a**–Cu–laponite catalyst has converted 137 molecules of THF to the products, with an average enantioselectivity of 82.5% ee for the syn isomers.

This enhancement in the selectivities is again in agreement with our previous results, as this same ligand showed the largest confinement effect in the case of cyclopropanation reactions.^{14b,15} We previously showed that surface effects were due to the close proximity of the catalytic complex, and this proximity can be increased by using solvents with low dielectric constants.¹⁴ In view of this, we tried to enhance the surface effect by carrying out the reaction in hexane. The detrimental effect of solvent on the yield was less marked than in the case of the homogeneous catalysts, with only marginal reductions. The enantioselectivity was slightly better in all cases. The most relevant effect was observed with azabox **2a**, leading to 71% ee in comparison with 58% ee obtained in THF. Box **1a** gave the highest enantiomeric excess, 88% ee in the first reaction.

In conclusion, readily accessible Cu(II) complexes easily immobilized on a cheap support promote insertion of carbenes into C–H bonds, with enantioselectivities up to 88% ee. This result demonstrates not only how immobilization is a method to recover and reuse the catalyst but also how the appropriate selection of support, immobilization method, and chiral catalyst enables an improvement in the catalytic performance, in terms of both yield and enantioselectivity. New experiments are underway to expand the scope of the reaction and to study its stereochemical course.

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Supporting Information Available: Full characterization of ligands, reagent, and products, catalytic reactions, and chromatographic methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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