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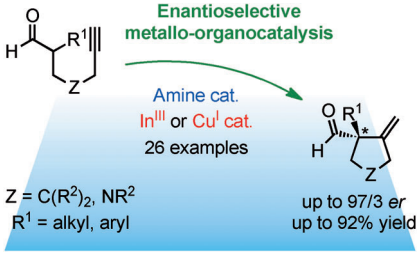

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DOI: 10.1002/cctc.201300313

Enantioselective Merger of Aminocatalysis with π-Lewis Acid Metal Catalysis: Asymmetric Preparation of Carbo- and Heterocycles

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The metallo-organocatalyzed enantioselective synthesis of various five-membered carbo- and heterocyclic structures through the merger of aminocatalysis with the catalytic indium(III) or copper(I) activation of α-disubstituted formyl alkynes is described. The use of indium trichloride associated with the (R)-1,1′-bis-(2-naphthylamine) ligand led to encouraging results with up to 85:15 enantiomeric ratio. After a careful examination of several other strategies, the best synergic catalytic system, which combines a chiral copper(I) complex with cyclohexylamine, afforded the enantioselective preparations of cyclopentane, indane, and pyrrolidine scaffolds with moderate to excellent control of the all-carbon quaternary stereogenic centers created through such cyclization processes.

Introduction

In the last five years, we have witnessed a tremendous expansion of new catalytic processes based on the use of two or more catalysts that act in a synergic manner.[1] Such a strategy has led not only to the discovery of original reactivity that would not occur under the action of a single catalyst but also to new ways of controlling enantioselectivity.[1,2] The specific cooperative association of a metal catalyst with an organocatalyst that takes place in "metallo-organocatalysis" prevails in this field, most probably owing to the opportunities offered by the combination of divergent activation modes.[3] In 2008, the pioneering work of Kirsch's and Dixon's groups demonstrated that upon treatment with catalytic quantities of both a secondary amine and a gold(I) or copper(I) metal complex, carbonyl alkynes could undergo racemic carbocyclization to cyclopentenes,[4] thus enlarging the scope of Conia–ene-type reactions, the vast majority of which rely on the involvement of enolates.[5] Since then, this original concept of merging amino catalysis to π-Lewis metal catalysis was applied to the preparation of various carbo- and heterocyclic skeletons, such as cyclopentenes, dihydrofurans, and dihydropyrroles.[6] Unfortunately, in all these processes,[4,6] the resulting exocyclic double bond undergoes internal isomerization, which in turn results in the destruction of the α-formyl stereogenic center formed via the key metallo-organocatalyzed cyclization step. Thus, we became involved in a related metallo-organocatalysis approach to carbo- and heterocyclic systems and focused our investigations on the carbocyclization reactions of α-disubstituted formyl alkynes. The presence of the extra substituent in the α position relative to the aldehyde residue prevents the occurrence of any isomerization and thus enables the retention of a valuable all-carbon quaternary stereogenic center.[7] In the last few years, we validated this metallo-organocatalytic approach and applied it to the racemic preparation of various cyclopentanes, indanes, pyrrolidines, and furans while merging the use of an amine catalyst either with a catalytic quantity of indium(III) chloride or with an in situ generated copper(I) complex.[8]

Since then, our efforts have been devoted to the development of an unprecedented enantioselective version of these metallo-organocatalytic carbocyclizations as it would offer new perspectives for the long-standing challenging control of all-carbon quaternary stereogenic centers.[9] We reported that the use of a catalytic chiral copper(I) complex in union with a catalytic primary amine enabled the preparation of enantioenriched cyclopentanes in good to excellent yields and enantioselectivities.[10] Herein, we report in full details asymmetric metallo-organocatalysis with indium- and copper-based catalytic systems, which leads to the preparation of various enantioenriched carbo- and heterocyclic systems (Scheme 1).

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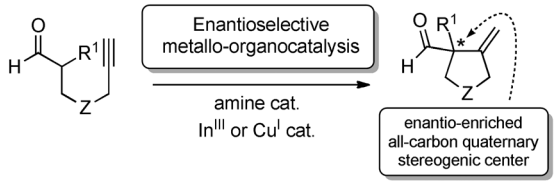
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201300313.

Results and Discussion

Indium(III)-based enantioselective metallo-organocatalytic system

At the beginning of this study, we turned our investigations to the discovery of an indium-based enantioselective metallo-organocatalytic system. As few examples of indium(III)-catalyzed asymmetric transformations have been described thus far, such



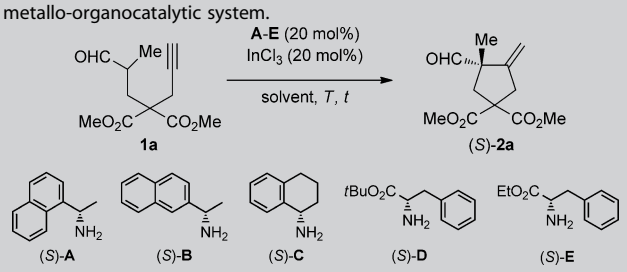
Scheme 1. Asymmetric metallo-organocatalysis with indium- and copper-based catalytic systems; the aim of this work. R^1 = alkyl, aryl; Z = $C(R^2)_2$, NR^2.

an approach was challenging.[11,12] We demonstrated previously that indium(III) chloride with a primary amine, such as cyclohexylamine, selectively promoted the carbocyclization of α-disubstituted formyl alkynes through an enamine-type mechanism whereas a secondary amine partly induced an undesirable enolate cyclization pathway.[8b] For this reason, we initially envisioned that the use of chiral primary amine organocatalysts could induce appreciable enantioselectivity in such carbocyclization processes. Thus, we selected a set of chiral primary amines **A**–**E**, which possess various electronic and steric properties and were commercially available, in the indium-mediated enantioselective carbocyclization of the model formyl alkyne **1a** (Table 1).

In the presence of indium trichloride (20 mol%), the screening of chiral primary amines **A**–**E** (20 mol%) was realized, together with the optimization of several parameters such as reaction temperature and solvent. The use of (*S*)-1-(1-naphthyl)ethylamine [(*S*)-**A**] as a chiral organocatalyst enabled us to obtain cyclopentane **2a** with weak, yet present, enantioselectivity (Table 1, entry 1). A progressive decrease in the reaction temperature from 100 to 20 °C resulted in a significant increase in enantiocontrol because **2a** could be isolated, after 40 h at 20 °C, in an encouraging 68:32 enantiomeric ratio (*er*; Table 1, entries 2 and 3). Under these latter reaction conditions, some other chiral amines were also tested, such as (*S*)-1-(2-naphthyl)ethylamine [(*S*)-**B**], (*S*)-1,2,3,4-tetrahydro-1-naphtalenamine [(*S*)-**C**], and phenylalanine ester derivatives (*S*)-**D** and (*S*)-**E**; however, none increased enantioinduction (Table 1, entries 4–7). Consequently, selecting **A** as the most promising organocatalyst, a solvent screening was performed. Of the different solvents examined, dioxane proved to be the best, in terms of both isolated yield and *er*, but did not bring any significant improvement compared to 1,2-dichloroethane [(DCE); Table 1, entries 8–12]. At this point, we decided to alternatively induce enantioselectivity through the use of chiral indium complexes.

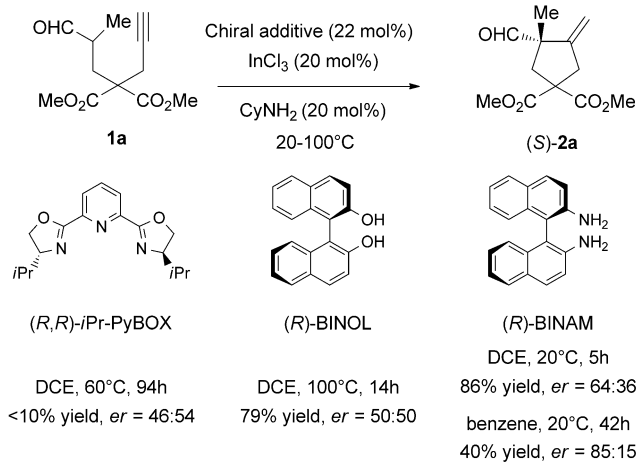
By studying the carbocyclization of **1a** with cyclohexylamine (20 mol%) as an organocatalyst and indium trichloride (20 mol%) in DCE, we evaluated (*R*,*R*)-isopropyl-pyridine-2,6-bis(oxazoline) (PyBOX) and (*R*)-1,1′-bi-2-naphthol as chiral additives (22 mol%) because both are used frequently in asymmetric indium(III)-catalyzed carbonyl–ene, Mukayama aldol, and allylation reactions (Scheme 2).[12]

Table 1. Evaluation of chiral primary amines with the indium(III)-based metallo-organocatalytic system.



Entry	Amine	Solvent	*T* [°C]	*t* [h]	Yield[a] [%]	Enantiomeric ratio[b] [*S*/*R*]
1	(*S*)-**A**	DCE	100	3	92	59:41
2	(*S*)-**A**	DCE	60	4	92	63:37
3	(*S*)-**A**	DCE	20	40	87	68:32
4	(*S*)-**B**	DCE	20	90	18	55:45
5	(*S*)-**C**	DCE	20	15	12	53:47
6	(*S*)-**D**	DCE	20	87	18	41:59
7	(*S*)-**E**	DCE	20	82	18	37:63
8	(*S*)-**A**	toluene	20	45	30	55:45
9	(*R*)-**A**	CH_2Cl_2	20	40	27	38:62
10	(*R*)-**A**	Et_2O	20	23	41	41:59
11	(*R*)-**A**	THF	20	28	68	35:65
12	(*R*)-**A**	dioxane	20	67	83	32:68

[a] Isolated yield; [b] Determined by using HPLC Chiralpak IC 80:20 hexane/*i*PrOH.

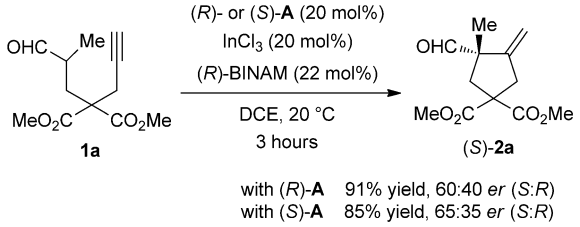


Scheme 2. Evaluation of a chiral indium catalyst-based strategy.

However, none of these two chiral additives enabled us to induce encouraging enantioselectivities (*er* < 46:54). Conversely, the use of the more Lewis basic diamino analogue of (*R*)-1,1′-bi-2-naphthol, (*R*)-1,1′-bis-(2-naphthylamine) ((*R*)-BINAM), which has demonstrated previously its usefulness in the coordination of metal complexes,[13] enabled the formation of cyclopentane **2a** in 86% yield and encouraging 64:36 *er* in only 5 h at room temperature (Scheme 2). After a careful examination of solvent effects, benzene proved to be more suitable for this enantioselective transformation because, despite the inferior reaction rate, carbocycle **2a** was isolated in encouraging 85:15 *er* (Scheme 2). Notably, the primary amino groups of BINAM proved to be essential for inducing good enantioselectivity and reactivity because, under identical reaction conditions, the use of the *N*,*N*′-bisphenyl analogue of BINAM[14]

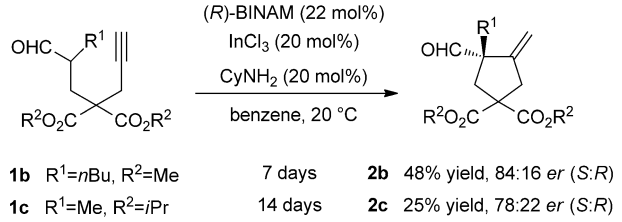
caused the sluggish formation of **2a** as a racemate (48 h, 22% yield).

Next, we investigated the opportunity offered by metallo-organocatalysis to merge a chiral organocatalyst with a chiral metal catalyst.[2] Considering the enantioselectivity generated with (*S*)-1-(1-naphthyl)ethylamine [(*S*)-**A**; Table 1, entry 3], we combined the catalytic use of this amine in either of its enantiomeric forms with the indium(III) chloride–(*R*)-BINAM catalytic system in DCE at 20 °C. Although in both cases cyclopentane **2a** was obtained in good yields, this dual chiral induction strategy was disappointing because lower enantioselectivities were obtained (Scheme 3).



Scheme 3. Evaluation of a dual chiral induction strategy.

Consecutively, the effect of the starting formyl alkyne was assessed with the α-butyl-substituted aldehyde **1b** and the diisopropylmalonate derivative **1c** (Scheme 4). Under the best



Scheme 4. Evaluation of the enantioselective indium-based catalytic system for aldehydes **1b** and **c**.

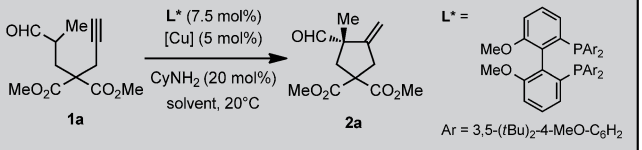
optimized conditions, with cyclohexylamine (20 mol%), indium(III) chloride (20 mol%), and (*R*)-BINAM (22 mol%) in benzene at 20 °C, both substrates showed moderate reactivity and did not yield **2b** or **c** in enantioselectivities higher than that of **2a**, which indicates a limited substrate scope for this enantioselective catalytic system.

Therefore, even if we could obtain up to 70% *ee* through the use of enantiopure BINAM additive, both the reactivity and the level of chiral induction generated by such an indium-based metallo-organocatalytic system were not fully satisfactory. With cyclohexylamine as an organocatalyst, we demonstrated that indium(III) chloride could be efficiently substituted with a copper(I) complex, which resulted in a mild catalytic system promoting the room temperature preparation of a large range of carbo- and heterocyclic rings.[8d] Thus, we decided to investigate the possibility of using an alternative copper(I)-based metallo-organocatalytic system for this enantioselective transformation.

Copper(I)-based enantioselective metallo-organocatalytic system

Taking into account that the racemic process relies on the in situ generation of a copper(I) metal catalyst through the reduction of copper(II) triflate with achiral triphenylphosphine,[8c,d] we evaluated various chiral mono- and bidentate phosphorous ligands. This screening revealed that such a metallo-organocatalyzed carbocyclization process requires sterically demanding diphosphine ligands to induce significant enantioinduction. The most promising result was obtained with 7.5 mol% of (*R*)-3,5-di-*tert*-butyl-4-methoxyphenyl-MeOBIPHEP[15] (**L***; MeOBIPHEP = (6,6′-dimethoxybiphenyl-2,2′-diyl)-bis(diphenylphosphine)) with which, in conjunction with 5 mol% of $Cu(OTf)_2$ (Tf = trifluoromethanesulfonyl) and 20 mol% of cyclohexylamine in DCE at 20 °C, **2a** was isolated in encouraging 11.5:88.5 *er* and excellent 95% yield (Table 2, entry 1). After conserving **L***, we performed the optimization of several reaction parameters such as the catalytic copper source and the solvent medium (Table 2).

Table 2. Optimization of the copper-based enantioselective catalytic system.



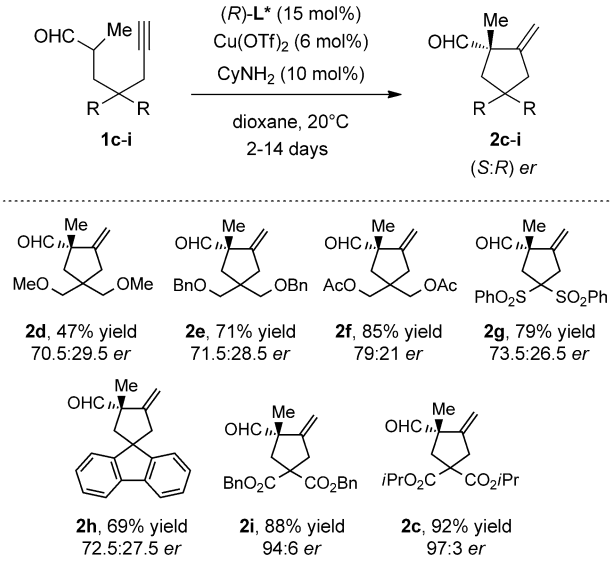
Entry	[Cu]	L*	Solvent	t [h]	Yield[a] [%]	Enantiomeric ratio[b] [S/R]
1	$Cu(OTf)_2$	(*S*)	DCE[c]	16	95	11.5:88.5
2[d]	$Cu(OTf)_2$	(*S*)	DCE	90	63	10:90
3[e]	CuTC[f]	(*S*)	DCE	70	40	41.5:58.5
4[e]	$Cu(CH_3CN)_4BF_4$	(*S*)	DCE	87	32	17.5:82.5
5[e]	CuOTf·0.5 benzene	(*R*)	DCE	168	63	69:31
6[e]	CuCl + AgOTf	(*S*)	DCE	62	40	21.5:78.5
7	$Cu(OTf)_2$	(*S*)	CH_2Cl_2	17	90	14:86
8	$Cu(OTf)_2$	(*S*)	MeOH	40	44	23:77
9	$Cu(OTf)_2$	(*S*)	AcOEt	72	63	15.5:84.5
10[e]	$Cu(OTf)_2$	(*S*)	Et_2O	67	44	13.5:86.5
11	$Cu(OTf)_2$	(*S*)	benzene	48	50	9.5:90.5
12	$Cu(OTf)_2$	(*S*)	THF	72	77	9.5:90.5
13	$Cu(OTf)_2$	(*S*)	dioxane	65	52	7:93
14[g]	$Cu(OTf)_2$	(*R*)	dioxane	29	84	92.5:7.5
15[g,h]	$Cu(OTf)_2$	(*R*)	dioxane	29	88	93.5:6.5

[a] Isolated yield; [b] Determined by using HPLC Chiralpak IC 80:20 hexane/*i*PrOH; [c] DCE = 1,2-Dichloroethane; [d] Reaction performed at 10 °C; [e] **L*** (5 mol%); [f] Copper(I)-thiophene-2-carboxylate; [g] $Cu(OTf)_2$ (6 mol%) with **L*** (15 mol%); [h] Cyclohexylamine (10 mol%).

A decrease in the reaction temperature to 10 °C resulted in a dramatic decrease in the cyclization rate but without any substantial improvement in the enantioselectivity (Table 2, entry 2). In contrast, switching from the copper(II) triflate pre-catalyst to copper(I) sources such as copper(I)-thiophene-2-carboxylate, tetrakis(acetonitrile) copper(I) tetrafluoroborate, the air-sensitive copper(I) triflate·0.5 benzene complex, or copper(I) chloride in the presence of an equimolar amount of silver tri-

flate was detrimental to enantioselectivity and/or yield (Table 2, entries 3–6). Thus, the in situ generation of the chiral copper(I) catalyst starting from $Cu(OTf)_2$ and **L*** appeared to be the best option. Notably, by using a dual chiral induction strategy, with each enantiomer of 1-(1-naphthyl)ethylamine (**A**) as an organocatalyst, no significant improvement could be observed in enantiocontrol. Of the various solvents then tested (Table 2, entries 7–13), even though at the expense of the cyclization rate, dioxane significantly improved the enantioselectivity of the catalytic system because **2a** was obtained in 7:93 *er* (Table 2, entry 13). The lack of reactivity associated with the use of dioxane could be circumvented with 6 mol% of $Cu(OTf)_2$, 15 mol% of **L***, and either 20 or 10 mol% of cyclohexylamine (Table 2, entries 14 and 15). In the latter case, cyclopentane **2a** was obtained in 88% yield and 93.5:6.5 *er* after 29 h at 20 °C (Table 1, entries 15).[16]

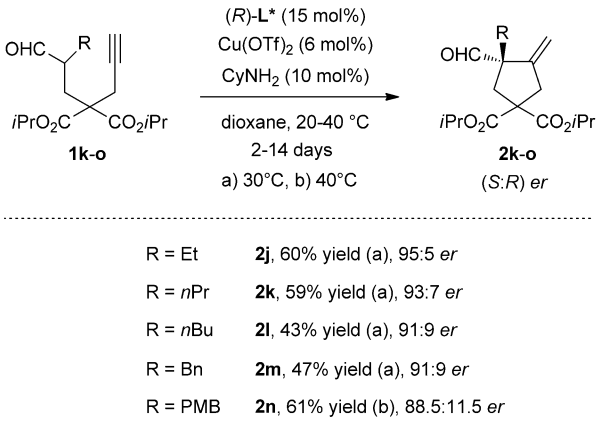
We then evaluated this enantioselective catalytic system in the preparation of a larger range of chiral cyclopentanes under the optimized reaction conditions. While investigating the carbocyclization of different α-methyl-substituted substrates (Scheme 5), the nature of the linkage existing between the formyl and alkyne moieties proved to have a substantial effect



Scheme 5. Scope of the enantioselective metallo-organocatalytic preparation of α-methyl-substituted cyclopentanes.

on the enantioselectivity. Replacing the dimethylmalonate linkage by less sterically hindered tethers such as *gem*-dimethoxymethyl, *gem*-dibenzyloxymethyl, or *gem*-diacetoxymethyl resulted in inferior enantiocontrol during the carbocyclization process. Thus, cyclopentanes **2d–f** were obtained in *er* values ranging from 70.5:29.5 to 79:21. Comparable enantioselectivities were obtained with *gem*-diphenylsulfonyl (**2g**) or 9-fluorenyl (**2h**) linkages, although they were more sterically hindered. The reaction of *gem*-dibenzyl malonate (**1i**) or *gem*-diisopropyl malonate (**1c**), the hindered ester moieties of which probably favor an enhanced steric interaction with the copper(I) π-complex, led to the formation of cyclopentanes **2i** and **c** in higher enantiopurity, reaching excellent *er* values of 94:6 and 97:3, respectively (Scheme 5).

Conversely, the effect of the α-formyl group on the enantioselectivity was assessed by studying the enantioselective carbocyclization of diisopropylmalonate substrates **1j–n** (Scheme 6). As a general trend, the bulkier substituent α to the aldehyde moiety induced longer reaction time as well as

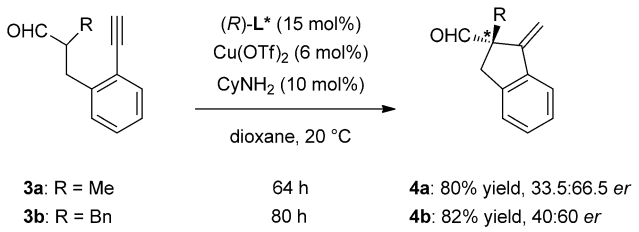


Scheme 6. Extended scope of the enantioselective cyclization of carbon-tethered substrates. PMB = *p*-methoxybenzyl group, $CyNH_2$ = cyclohexylamine.

a moderate decrease in enantiocontrol. Thus, the α-ethyl-substituted cyclopentane **2j** was obtained after 14 days at 30 °C in 60% yield and 95:5 *er*. The gradual increase in the steric demand of the substituent next to the aldehyde moiety progressively weakened the enantioselectivity. The switch from an ethyl group to an *n*-propyl, *n*-butyl, benzyl, and *p*-methoxybenzyl residue resulted in the *er* values from 95:5 (**2j**) to 88.5:11.5 (**2n**). Hence, if the enantioselective preparation of cyclopentanes is considered, high enantioselectivities could be obtained through the use of sterically demanding formyl-alkyne tethers, an effect that could be partially counterbalanced if larger groups are introduced in the α position of the aldehyde moiety.

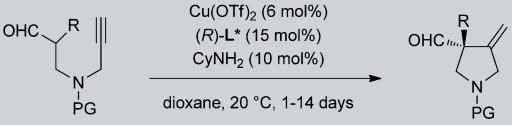
Aromatic tethered formyl alkynes **3a,b** were also submitted to enantioselective cyclization, and in both cases, indanes **4a,b** were obtained in good yields. However, disappointing enantioselectivities were obtained for this class of compounds, which highlighted the prominent effect of the aldehyde/alkyne linkage on stereoinduction (Scheme 7).

We demonstrated previously that the mild reaction conditions arising from the use of a copper-based metallo-organocatalytic system enabled the efficient preparation of racemic pyrrolidines.[8d] Thus, several nitrogen-tethered substrates **5a–j** were submitted to the optimized enantioselective reaction conditions as it would enable the preparation of the corresponding valuable enantioenriched nitrogen heterocycles (Table 3).[17] By starting with the *N*-tosyl-protected α-methyl aldehyde **5a**, the desired pyrrolidine product **6a** was isolated in 91% yield and 78:22 *er* after 1 day at 20 °C (Table 3, entry 1).



Scheme 7. Enantioselective preparation of indanes.

Table 3. Enantioselective metallo-organocatalytic preparation of pyrrolidines.



5a-j **6a-j**

Entry	R	PG[a]	Product, yield[b] [%]	Enantiomeric ratio[c] [*S*/*R*]
1	Me	Ts[d]	**6a**, 91	78:22
2	*n*Bu	Ts	**6b**, 84	72.5:27.5
3	Bn[e]	Ts	**6c**, 80	69.5:30.5
4	PMB	Ts	**6d**, 81	72.5:27.5
5	$(CH_2)_2OBn$	Ts	**6e**, 86	75.5:24.5
6	Ph	Ts	**6f**, 87	62.5:37.5
7	Me	Ns[f]	**6g**, 82	80:20
8	*n*Bu	Ns	**6h**, 91	73.5:26.5
9	Me	SO_2-2,3,5-$(Me)_3C_6H_2$	**6i**, 88	85.5:14.5
10	Me	SO_2-2,3,5-$(iPr)_3C_6H_2$	**6j**, 81	83:17

[a] Protecting group; [b] Isolated yield; [c] Determined by using chiral stationary phase HPLC; [d] Tosyl; [e] Benzyl; [f] Nosyl.

Similar to the enantioselective synthesis of cyclopentanes (Scheme 6), hindering the α position relative to the aldehyde moiety resulted in a significant decrease in the reaction rate as well as a notable decrease in stereoselectivity. Thus, pyrrolidines **6b–e**, which showed *n*-butyl, benzyl, *p*-methoxybenzyl, and benzyloxyethyl residues, respectively, required prolonged reaction times, 9–14 days at 20 °C, and were isolated in good 80–86% yields and *er* values ranging from 69.5:30.5 to 75.5:24.5 (Table 2, entries 2–5). The poorer enantioselectivity for this class of compounds was obtained by starting with the α-phenyl substrate **5f**, with which the corresponding heterocycle **6f** was obtained in 62.5:37.5 *er* (Table 2, entry 6). Next, we tested the use of *N*-nosyl-substituted substrates **5g**,**h**, as such an N-protecting group undergoes cleavage under milder reaction conditions compared to those required for the *N*-tosyl parent.[18] The corresponding *N*-nosyl pyrrolidines **6g**,**h** could be isolated in good yields and enantioselectivities, which were close to those obtained for *N*-tosyl pyrrolidines **6a**,**b** (Table 2, entries 7 and 8).

Thereafter, the beneficial effect of steric hindrance generated by the aldehyde–alkyne linkage on the enantioselectivity observed during the investigation of the enantioselective preparation of cyclopentanes led us to consider the use of more sterically demanding sulfonyl groups on the nitrogen atom. Thus, the *N*-2,3,5-trimethylbenzene-sulfonyl and *N*-2,3,5-tri(isopropyl)-benzenesulfonyl substrates **5i**,**j** were prepared and submitted to cyclization. Such modification of the substrate structure enabled the formation of trimethylphenylsulfonyl pyrrolidine **6i** with an improved 85.5:14.5 *er* (Table 2, entry 9), which could not be improved further with the triisopropyl analogue **5j** (Table 2, entry 10). Therefore, nitrogen-tethered substrates were also good partners in this enantioselective copper(I)-based metallo-organocatalyzed carbocyclization process even if the enantioselectivity obtained for this class of compounds was lower than that obtained with the carbon-tethered substrates. Hence, not only the steric hindrance but also the geometry (sp^2 versus sp^3) of the aldehyde–alkyne linkage proved to have a substantial effect on enantioinduction.

Proposition of a model for enantioselectivity

Previous studies on the racemic copper(I) metallo-organocatalyzed cyclization of formyl alkynes led us to propose a chair-like transition state in which the C–C bond formation process, the rate-determining step of the reaction, stems from the *anti*-attack of an organocatalytically formed enamine onto the alkyne moiety activated by a copper(I) complex.[19,20] After the reasonable assumption that the use of chiral ligands on the copper(I) catalyst does not change this effect, we suggest that the cyclization step could then occur according to four diastereoisomeric intermediates **I**–**IV**, depending on the facial approach of the enamine residue as well as the pseudo-axial or pseudo-equatorial position occupied by the R group in the α position of the initial aldehyde moiety (Figure 1).

On the basis of the significant effect of the bulkiness of the R group on both the racemic and enantioselective cyclization rates, we are inclined to believe that the R group occupies a pseudo-axial (Figure 1, **I** and **II**) rather than a pseudo-equatorial position (Figure 1, **III** and **IV**). The enhanced 1,3-diaxial strains in **I** and **II** associated with a larger R substituent would account for the slower reactivity observed experimentally. By studying the enantioselective preparation of cyclopentanes, we determined that with the *R* enantiomer of the ligand **L***, the major enantiomer of **2c** possesses the *S* configuration.[10] Hence, **L*** would favor either intermediate **I** or **IV** (Figure 1). Therefore, we suggest that with (*R*)-**L***, the cyclization process should preferentially occur according to intermediate **I**. In continuation to this hypothesis, the effect on the enantioselectivity of the steric hindrance generated by the Y groups, which was observed in the cyclopentane series, led us to postulate that enantiodiscrimination would arise from steric interactions between the chiral copper(I) complex and the Y groups of the aldehyde–alkyne linkage.

Thus, we propose the following model of enantioselectivity in which the bulky ligand **L*** would impose a quadrant-like steric environment around the triple bond, which results from a pseudo-trigonal planar geometry around the copper atom (Figure 2).[21,22] As a result, the cyclization precursor would in-

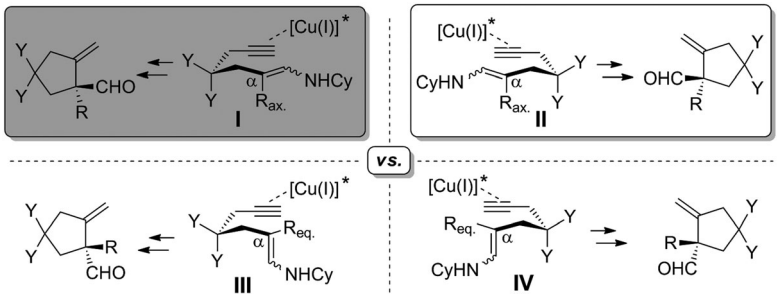


Figure 1. Hypothetical cyclization intermediates.

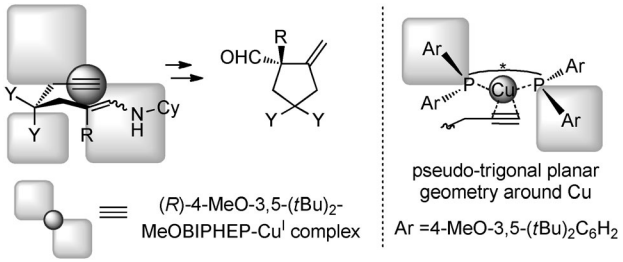
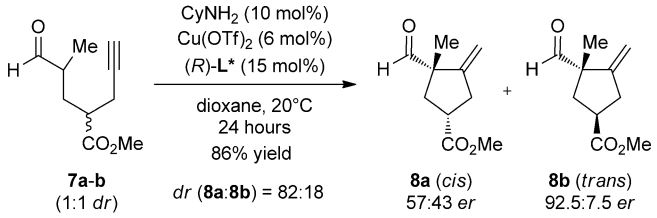


Figure 2. Proposition of a model for the enantioselectivity.

Finally, the little difference of enantiopurity observed between the cyclopentane monoester **8b** (92.5:7.5) and the malonyl cyclopentane **2a** (93.5:6.5; Table 1, entry 11) was consistent with our proposal that regardless of the nature of the pseudo-equatorial substituent, chiral induction relies principally on steric repulsions between the chiral copper(I) catalyst and the pseudo-axial group present on the aldehyde–alkyne backbone.



Scheme 8. Enantioselective cyclization of a dissymmetrical formyl alkyne **7a**,**b**. *dr* = Diastereomeric ratio.

teract with the copper(I) complex to preferentially enable the pseudo-axial substituent Y to remain in the vacant residual space (Figure 2). In addition, this model is empirically supported by the fact that both pyrrolidine and indane precursors led to inferior stereoselectivities as the associated sp^2 geometry of the tether probably hampers an equally efficient enantiodiscrimination. It also clarified the necessity of using much sterically hindered phosphorous ligands such as **L***.

To further confirm this model, we performed the enantioselective cyclization of the dissymmetrical tethered formyl alkyne **7a**,**b** (1:1 mixture of diastereoisomers; Scheme 8). Such a cyclization precursor resulted in the formation of diastereoisomeric cyclopentanes **8a**,**b** with divergent enantiopurities. Although the major *cis* isomer **8a** was formed as an racemic mixture (57:43 *er*), the minor *trans* isomer **8b** was obtained in 92.5:7.5 *er*, which is close to that of dimethylmalonate analogous cyclopentane **2a** (93.5:6.5 *er*; Table 1, entry 11).[23] These results fit the abovementioned proposed model in many ways. First, the significant diastereoselectivity in favor of the *cis* isomer was consistent with a chair-like transition state, in which the α-methyl group stands in the pseudo-axial position whereas the methyl ester moiety was preferentially in the pseudo-equatorial position (Figure 3a and b). Second, in the case of **8a**, the presence of a small pseudo-axial hydrogen atom does not allow inducing good enantioselectivity (Figure 3a). During the formation of **8b**, a better differentiation of the two diastereoisomeric transition states was observed because the more hindered pseudo-axial methyl ester residue preferentially occupied the region of space free from interactions with the chiral copper(I) complex (Figure 3b).

Conclusions

We report a detailed study of the enantioselective metallo-organocatalyzed cyclization of formyl alkynes. Various chiral induction strategies based on the use of catalytic indium(III) or copper(I) metal complexes associated with primary amine organocatalysts were carefully examined. Although some level of enantioinduction could be obtained with a catalytic system based on indium(III) chloride, enantiopure (R)-1,1′-bis-(2-naphthylamine) ligand, and cyclohexylamine, this approach was limited in terms of enantioselectivity, reactivity, and substrate scope. Conversely, we demonstrated the superiority of a copper(I) alternative, in which the catalytic synergy between a chiral copper(I) complex and cyclohexylamine opened access

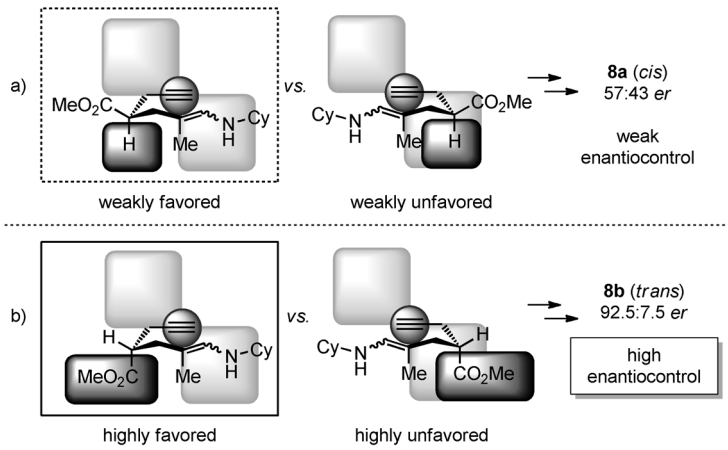


Figure 3. Enantioselectivity model rationale.

to the preparation of various enantioenriched five-membered carbo- and heterocyclic systems with fair to excellent enantioselectivities and yields. Finally, several factors governing the challenging control of the all-carbon quaternary stereogenic center created during such cyclization processes were unveiled, on the basis of which an empirical model for enantioselectivity was proposed.

Experimental Section

General

^{1}H NMR and ^{13}C NMR signals were internally referenced to residual protio solvent signals. High-resolution mass spectra were performed on a LTQ Orbitrap apparatus. All solvents used herein were purified according to literature methods.[24] Enantiomeric ratios were determined by using chiral stationary phase HPLC (CSP-HPLC) with OD-H, OJ, IA, IB, IC, or ID columns and *n*-hexane/*i*PrOH mixtures as mobile phases.

Materials

The preparation of most of the aldehyde substrates used herein has been described previously by us.[8a–d] New aldehyde substrates **1h**, **1n**, **5d**,**g–j**, **7a**,**b** were prepared by analogy to the corresponding published methods.

2-Methyl-3-(9-(prop-2-yn-1-yl)-9H-fluoren-9-yl)propanal (**1h**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (d, J = 2.2 Hz, 1H), 7.82–7.67 (m, 2H), 7.65–7.50 (m, 2H), 7.48–7.27 (m, 4H), 2.91 (dd, J = 14.2, 7.0 Hz, 1H), 2.65 (d, J = 2.6 Hz, 2H), 2.22 (dd, J = 14.2, 4.8 Hz, 1H), 2.07 (t, J = 2.7 Hz, 1H), 1.62–1.43 (m, 1H), 0.68 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.4, 148.5, 147.8, 140.8, 140.6, 128.3, 128.1, 127.5, 124.0, 123.6, 120.3, 120.2, 81.1, 71.1, 51.8, 42.8, 38.0, 30.7, 15.6 ppm.

Diisopropyl 2-(2-formyl-3-(4-methoxyphenyl)propyl)-2-(prop-2-yn-1-yl)malonate (**1n**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56 (d, J = 2.7 Hz, 1H), 7.15–6.99 (m, 2H), 6.88–6.72 (m, 2H), 5.08–4.87 (m, 2H), 3.77 (s, 3H), 2.96–2.65 (m, 5H), 2.61–2.47 (m, 1H), 2.12 (dd, J = 14.8, 2.2 Hz, 1H), 1.95 (t, J = 2.7 Hz, 1H), 1.32–1.07 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.5, 169.5, 169.4, 158.5, 130.3, 129.7, 114.1, 78.6, 72.0, 69.7, 69.6, 56.0, 55.4, 49.5, 36.6, 30.9, 27.0, 23.6, 21 ppm; HRMS (ESI): *m/z*: calcd for $C_{23}H_{30}O_6Na$: 425.1935 $[M+Na]^+$; found: 425.1941.

N-(2-Formyl-3-(4-methoxyphenyl)propyl)-4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**5d**): Sticky colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (d, J = 1.7 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 4.01 (d, J = 2.1 Hz, 2H), 3.70 (s, 3H), 3.43–3.30 (m, 1H), 3.17–3.00 (m, 2H), 2.88 (dd, J = 14.3, 7.0 Hz, 1H), 2.66 (dd, J = 14.3, 6.9 Hz, 1H), 2.32 (s, 3H), 1.93 ppm (t, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.0, 158.5, 143.9, 134.8, 130.0, 129.6, 129.4, 127.9, 114.2, 76.4, 74.3, 55.3, 52.4, 45.6, 38.1, 32.7, 21.6 ppm; HRMS (ESI): *m/z*: calcd for $C_{21}H_{24}NO_4S$: 386.1421 $[M+H]^+$; found: 386.1427.

N-(2-Methyl-3-oxopropyl)-4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (**5g**): Yellow paste; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (d, J = 1.4 Hz, 1H), 8.34 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.6 Hz, 2H), 4.18 (d, J = 2.4 Hz, 2H), 3.52 (dd, J = 14.3, 7.5 Hz, 1H), 3.23 (dd, J = 14.3, 6.7 Hz, 1H), 2.91–2.73 (m, 1H), 2.04 (t, J = 2.5 Hz, 1H), 1.19 ppm (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.5, 150.3, 144.1, 129.2, 124.3, 75.6, 75.0, 47.0, 45.3, 37.7, 11.9 ppm.

N-(2-Formylhexyl)-4-nitro-*N*-(prop-2-ynyl)benzenesulfonamide (**5h**): Yellow paste; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.71–9.58 (m, 1H), 8.41–8.25 (m, 2H), 8.02 (d, J = 8.5 Hz, 2H), 4.29–4.05 (m, 2H), 3.54 (dd, J = 14.2, 8.7 Hz, 1H), 3.22 (dd, J = 14.2, 5.7 Hz, 1H), 2.85–2.64 (m, 1H), 2.03 (t, J = 2.4 Hz, 1H), 1.80–1.59 (m, 1H), 1.59–1.43 (m, 1H), 1.43–1.19 (m, 4H), 0.98–0.79 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8, 150.3, 144.0, 129.2, 124.2, 75.6, 75.0, 50.5, 45.5, 37.5, 28.7, 26.9, 22.7, 13.8 ppm.

2,4,6-Trimethyl-*N*-(2-methyl-3-oxopropyl)-*N*-(prop-2-ynyl)benzenesulfonamide (**5i**): Colorless sticky oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.42 (d, J = 2.1 Hz, 1H), 6.96 (s, 2H), 4.09 (dd, J = 18.3, 2.3 Hz, 1H), 3.98 (dd, J = 18.3, 2.4 Hz, 1H), 3.58 (dd, J = 14.5, 8.0 Hz, 1H), 3.34 (dd, J = 14.5, 6.2 Hz, 1H), 2.79–2.65 (m, 1H), 2.59 (s, 6H), 2.37–2.24 (m, 4H), 1.05 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.8, 143.3, 140.6, 132.3, 131.9, 77.3, 74.0, 46.6, 44.9, 35.9, 23.0, 21.1, 12.2 ppm; HRMS (ESI): *m/z*: calcd for $C_{16}H_{22}NO_3S$: 308.1314 $[M+H]^+$; found: 308.1323.

2,4,6-Triisopropyl-*N*-(2-methyl-3-oxopropyl)-*N*-(prop-2-ynyl)benzenesulfonamide (**5j**): Colorless sticky oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.60 (d, J = 2.1 Hz, 1H), 7.17 (s, 2H), 4.15–3.87 (m, 4H), 3.73 (dd, J = 14.5, 8.0 Hz, 1H), 3.43 (dd, J = 14.5, 6.1 Hz, 1H), 2.99–2.76 (m, 2H), 2.30 (t, J = 2.5 Hz, 1H), 1.25 (d, J = 6.9 Hz, 18H), 1.13 ppm (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.9, 153.9, 152.0, 130.1, 124.3, 74.1, 46.1, 45.1, 36.5, 34.3, 29.6, 25.0, 23.7, 12.5 ppm; HRMS (ESI): *m/z*: calcd for $C_{22}H_{34}NO_3S$: 392.2254 $[M+H]^+$; found: 392.2263.

Methyl 2-(2-methyl-3-oxopropyl)pent-4-ynoate (**7a**,**b**): 1:1 mixture of diastereoisomers **7a**,**b**; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 9.60 (s, 1H), 3.7 (s, 6H), 2.78–2.62 (m, 2H), 2.62–2.33 (m, 6H), 2.29–2.12 (m, 1H), 2.12–1.96 (m, 3H), 1.85–1.68 (m, 1H), 1.69–1.51 (m, 1H), 1.15 (d, J = 6,5 Hz, 3H), 1.12 ppm (d, J = 6,5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 80.6, 70.5, 52.0, 44.2, 44.1, 41.9, 31.8, 31.6, 21.7, 14.0, 13.4 ppm; HRMS (ESI): *m/z*: calcd for $C_{10}H_{15}O_3$: 183.1016 $[M+H]^+$; found: 183.1018.

General method for the enantioselective copper(I) metallo-organocatalyzed cyclization

In a vial under argon atmosphere, (*R*)-4-MeO-3,5-(*t*Bu)$_2$-MeOBIPHEP (**L***; 0.03 mmol, 0.15 equiv.), copper(II) trifluoromethanesulfonate (0.012 mmol, 0.06 equiv.), and dioxane (0.15 mL) were added successively. The resulting mixture was stirred for 15 min at RT before freshly purified formyl alkyne (0.2 mmol, 1 equiv.) in a freshly prepared solution of cyclohexylamine (0.1 M, 0.1 mL) in dioxane (0.02 mmol, 0.1 equiv.) was added. After the introduction of additional dioxane (0.25 mL), the reaction mixture was stirred at the specified temperature until TLC analysis indicated complete conversion (see vide infra). The reaction mixture was then treated with an aqueous solution of acetic acid (1 mL, 1:1 v/v) and then vigorously stirred for 15 min at RT before the extraction of the aqueous layer with DCE. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting crude material was purified by using flash column chromatography to afford the pure carbo- or heterocyclic aldehyde. The enantioselective preparation of **2a**–**e**,**g**,**i**,**j**–**m** has been reported previously by us.[10]

(3-Formyl-3-methyl-4-methylenecyclopentane-1,1-diyl)bis(methylene) diacetate (**2f**):[8a] Prepared according to the above general protocol starting from **1f** (54.0 mg, 0.20 mmol) at 20 °C for 3 days. Colorless oil (46 mg, 69% yield); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.29 (s, 1H), 5.18 (t, J = 1.9 Hz, 1H), 4.97 (dd, J = 2.3, 1.7 Hz, 1H), 4.12–

3.80 (m, 4H), 2.55–2.16 (m, 3H), 2.06 (d, J=1.4 Hz, 6H), 1.43 (d, J=14.3 Hz, 1H), 1.29 ppm (s, 3H); CSP-HPLC (ID, *n*-hexane/*i*PrOH 80:20, 1 mL min^{-1}, 215 nm): *er*=79:21; t_R(major)=8.74 min, t_R(minor)=11.11 min; $[\alpha]_D^{20}=-44.7$ (c=0.42 in $CHCl_3$).

3-Methyl-4-methylenespiro[cyclopentane-1,9′-fluorene]-3-carbaldehyde (**2h**): Prepared according to the above general protocol starting from **1h** (55.0 mg, 0.20 mmol) at 20 °C for 14 days. Yellow oil (38 mg, 69% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.56 (s, 1H), 7.77–7.66 (m, 2H), 7.66–7.58 (m, 1H), 7.52–7.44 (m, 1H), 7.41–7.27 (m, 4H), 5.30 (dd, J=2.3, 1.1 Hz, 1H), 5.20 (dd, J=2.3, 1.0 Hz, 1H), 3.17 (d, J=14.4 Hz, 1H), 2.93 (dt, J=15.3, 2.3 Hz, 1H), 2.67–2.54 (m, 1H), 1.98 (d, J=14.4 Hz, 1H), 1.56 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.9, 153.7, 152.7, 151.6, 139.8, 139.4, 127.9, 127.6, 127.4, 127.3, 123.5, 123.0, 119.9, 119.7, 110.2, 58.1, 54.2, 46.4, 44.8, 21.2 ppm; CSP-HPLC (OD-H, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er*=72.5:27.5; t_R(minor)=9.30 min, t_R(major)=11.93 min; $[\alpha]_D^{20}=+122.2°$ (c=1.0 in $CHCl_3$).

Diisopropyl-3-formyl-3-(4-methoxybenzyl)-4-methylenecyclopentane-1,1-dicarboxylate (**2n**): Prepared according to the above general protocol starting from **1n** (80.4 mg, 0.20 mmol) at 40 °C for 12 days. Yellow oil (49 mg, 61% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.45 (s, 1H), 7.06 (d, J=8.7 Hz, 2H), 6.79 (d, J=8.7 Hz, 2H), 5.29 (s, 1H), 5.13–4.90 (m, 3H), 3.77 (s, 3H), 3.12 (d, J=14.0 Hz, 1H), 3.00–2.89 (m, 1H), 2.83 (d, J=14.0 Hz, 1H), 2.74–2.63 (m, 2H), 2.42 (d, J=14.3 Hz, 1H), 1.25–1.14 ppm (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=199.9, 171.0, 170.7, 158.5, 148.7, 131.2, 128.8, 113.9, 111.1, 69.4, 69.3, 61.8, 58.3, 55.3, 41.6, 41.0, 36.5, 21.6 ppm; HRMS (ESI): *m/z*: calcd for $C_{23}H_{30}O_6Na$: 425.1935 $[M+Na]^+$; found: 425.1941; CSP-HPLC (IC, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er*=88.5:11.5; t_R(minor)=10.54 min, t_R(major)=13.77 min; $[\alpha]_D^{20}=+63.0$ (c=1 in $CHCl_3$).

2-Methyl-1-methylene-2,3-dihydro-1*H*-indene-2-carbaldehyde (**4a**):[8d] Prepared according to the above general protocol starting from **3a** (34.0 mg, 0.20 mmol) at 20 °C for 64 h. Colorless oil (27.2 mg, 80% yield); ^{1}H NMR (300 MHz, C_6D_6): δ=8.94 (s, 1H), 7.05–6.92 (m, 2H), 6.88–6.70 (m, 2H), 5.23 (s, 1H), 4.58 (s, 1H), 3.01 (d, J=16.8 Hz, 1H), 2.13 (d, J=16.8 Hz, 1H), 0.92 ppm (s, 3H); CSP-HPLC (after $NaBH_4$ mediated reduction in MeOH, OJ, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er*=65:35; t_R(minor)=7.24 min, t_R(major)=9.16 min.

2-Benzyl-1-methylene-2,3-dihydro-1*H*-indene-2-carbaldehyde (**4b**):[8d] Prepared according to the above general protocol starting from **3b** (50.0 mg, 0.20 mmol) at 20 °C for 80 h. Colorless oil (41 mg, 82% yield); ^{1}H NMR (300 MHz, C_6D_6): δ=9.28 (s, 1H), 7.26–7.17 (m, 1H), 7.11–6.81 (m, 8H), 5.53 (s, 1H), 4.87 (s, 1H), 3.21 (d, J=14.0 Hz, 1H), 3.11 (d, J=17.0 Hz, 1H), 2.73 (d, J=14.0 Hz, 1H), 2.70 ppm (d, J=17.0 Hz, 1H); CSP-HPLC (IC, *n*-hexane/*i*PrOH 95:5, 1 mL min^{-1}, 215 nm): *er*=61.5:38.5; t_R(minor)=5.66 min, t_R(major)=7.33 min.

3-Methyl-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6a**):[8a] Prepared according to the above general protocol starting from **5a** (55.8 mg, 0.20 mmol) at 20 °C for 1 day. Colorless solid (51 mg, 91% yield); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=9.29 (s, 1H), 7,31–7.22 (m, 2H), 7.38–7.34 (m, 2H), 5.21 (t, J=1.8 Hz, 1H), 5.01 (t, J=2.3 Hz, 1H), 3.88–3.84 (m, 2H), 3.80 (d, J=9.9 Hz, 1H), 3.03 (d, J=10.0 Hz, 1H), 2.04 (s, 3H), 1.24 ppm (s, 3H); CSP-HPLC (IA, *n*-hexane/*i*PrOH 70:30, 1 mL min^{-1}, 215 nm): *er*=78:22; t_R(minor)=8.66 min, t_R(major)=12.66 min; $[\alpha]_D^{20}=+30.1$ (c=1 in $CHCl_3$).

3-Butyl-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6b**):[8d] Prepared according to the above general protocol starting from **5b** (64.3 mg, 0.20 mmol) at 20 °C for 9 days. Colorless solid (54 mg, 84% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.22 (s, 1H), 7.72 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.0 Hz, 2H), 5.22 (s, 1H), 5.03 (t, J=1.8 Hz, 1H), 3.95–3.67 (m, 3H), 3.09 (d, J=10.0 Hz, 1H), 2.44 (s, 3H), 1.88–1.69 (m, 1H), 1.59–1.43 (m, 1H), 1.37–1.16 (m, 2H), 1.16–0.99 (m, 2H), 0.85 ppm (t, J=7.2 Hz, 3H); CSP-HPLC (IC, *n*-hexane/*i*PrOH 50:50, 1 mL min^{-1}, 215 nm): *er*=72.5:27.5; t_R(minor)=36.16 min, t_R(major)=30.84 min; $[\alpha]_D^{20}=+39.8$ (c=1 in $CHCl_3$).

3-Benzyl-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6c**):[8d] Prepared according to the above general protocol starting from **5c** (71.0 mg, 0.20 mmol) at 20 °C for 13 days. Colorless solid (50 mg, 80% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.30 (s, 1H), 7.57 (d, J=8.3 Hz, 2H), 7.34–7.04 (m, 5H), 7.01–6.87 (m, 2H), 5.21 (s, 1H), 5.04 (s, 1H), 3.79–3.57 (m, 2H), 3.46 (d, J=10.2 Hz, 1H), 3.17 (d, J=10.2 Hz, 1H), 3.15 (d, J=14.0 Hz, 1H), 2.76 (d, J=14.0 Hz, 1H), 2.36 ppm (s, 3H); CSP-HPLC (IA, *n*-hexane/*i*PrOH 70:30, 1 mL min^{-1}, 215 nm): *er*=69.5:30.5; t_R(minor)=7.76 i, t_R(major)=8.57 min; $[\alpha]_D^{20}=+17.7$ (c=1 in $CHCl_3$).

3-(4-Methoxybenzyl)-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6d**): Prepared according to the above general protocol starting from **5d** (77.0 mg, 0.20 mmol) at 20 °C for 13 days. Colorless oil (63.0 mg, 81% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.37 (s, 1H), 7.65 (d, J=8.2 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 6.94 (d, J=8.6 Hz, 2H), 6.75 (d, J=8.6 Hz, 2H), 5.27 (d, J=1.0 Hz, 1H), 5.10 (d, J=1.0 Hz, 1H), 3.85–3.73 (m, 5H), 3.52 (d, J=10.2 Hz, 1H), 3.25 (d, J=10.2 Hz, 1H), 3.16 (d, J=14.1 Hz, 1H), 2.79 (d, J=14.1 Hz, 1H), 2.44 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.7, 158.8, 144.4, 144.2, 132.2, 131.0, 129.8, 128.1, 127.7, 114.1, 111.5, 61.7, 55.3, 52.5, 51.5, 38.8, 21.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{21}H_{24}NO_4S$: 386.1421 $[M+H]^+$; found: 386.1426; CSP-HPLC (IA, *n*-hexane/*i*PrOH 70:30, 1 mL min^{-1}, 215 nm): *er*=72.5:27.5; t_R(minor)=8.58 min, t_R(major)=10.38 min; $[\alpha]_D^{20}=+19.2$ (c=1 in $CHCl_3$).

3-(2-(Benzyloxy)ethyl)-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6e**):[8d] Prepared according to the above general protocol starting from **5e** (79.8 mg, 0.20 mmol) at 20 °C for 14 days. Colorless solid (68.6 mg, 86% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.14 (s, 2H), 7.55 (d, J=8.3 Hz, 4H), 7.33–6.93 (m, 17H), 5.05 (s, 2H), 4.90 (s, 2H), 4.22 (s, 4H), 3.78–3.49 (m, 6H), 3.41–3.27 (m, 2H), 3.27–3.13 (m, 2H), 3.05 (d, J=10.1 Hz, 2H), 2.28 (s, 6H), 2.23–2.05 (m, 2H), 1.74–1.54 ppm (m, 2H); CSP-HPLC (IA, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er*=75.5:24.5; t_R(minor)=19.55 min, t_R(major)=26.14 min; $[\alpha]_D^{20}=+20.7$ (c=1 in $CHCl_3$).

3-Phenyl-4-methylene-1-tosylpyrrolidine-3-carbaldehyde (**6f**):[8d] Prepared according to the above general protocol starting from **5f** (68.2 mg, 0.20 mmol) at 20 °C for 14 days. Colorless solid (59.0 mg, 87% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.37 (s, 1H), 7.62 (d, J=8.3 Hz, 2H), 7.34–7.17 (m, 5H), 7.11–7.02 (m, 2H), 5.46 (s, 1H), 5.18–4.91 (m, 1H), 4.15 (d, J=9.9 Hz, 1H), 4.03–3.73 (m, 2H), 3.21 (d, J=9.9 Hz, 1H), 2.37 ppm (s, 3H); CSP-HPLC (IA, *n*-hexane/*i*PrOH 50:50, 1 mL min^{-1}, 215 nm): *er*=62.5:37.5; t_R(minor)=6.46 min, t_R(major)=12.16 min; $[\alpha]_D^{20}=-6.1$ (c=1 in $CHCl_3$).

3-Methyl-4-methylene-1-(4-nitrophenylsulfonyl)pyrrolidine-3-carbaldehyde (**6g**): Prepared according to the above general protocol starting from **5g** (70.4 mg, 0.23 mmol) at 20 °C for 10 days. Colorless sticky oil (58.0 mg, 82% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.19 (s, 1H), 8.48–8.32 (m, 2H), 8.09–7.97 (m, 2H), 5.27 (s, 1H), 5.15–5.06 (m, 1H), 4.02–3.91 (m, 2H), 3.86 (dt, J=13.9, 2.3 Hz, 1H), 3.09 (d, J=10.0 Hz, 1H), 1.26 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=196.8, 150.5, 144.2, 142.1, 129.0, 124.5, 111.6, 57.1, 53.5, 51.9, 18.1 ppm; HRMS (ESI): *m/z*: calcd for $C_{13}H_{15}N_2O_5S$: 311.0696 $[M+H]^+$; found: 311.0701; CSP-HPLC (IA, *n*-hexane/*i*PrOH 30:70,

1 mL min^{-1}, 215 nm): *er* = 80:20; t_R(minor) = 10.73 min, t_R(major) = 15.13 min; $[\alpha]_D^{20} = +31.9$ ($c = 1$ in $CHCl_3$).

3-Butyl-4-methylene-1-(4-nitrophenylsulfonyl)pyrrolidine-3-carbaldehyde (**6h**): Prepared according to the above general protocol starting from **5h** (70.4 mg, 0.20 mmol) at 20 °C for 14 days. Colorless solid (64.0 mg, 91% yield); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.12$ (s, 1H), 8.40 (d, $J = 8.8$ Hz, 2H), 8.03 (d, $J = 8.8$ Hz, 2H), 5.29 (s, 1H), 5.12 (s, 1H), 4.04–3.89 (m, 2H), 3.78 (dt, $J = 13.9$, 2.2 Hz, 1H), 3.19 (d, $J = 10.0$ Hz, 1H), 1.85 (ddd, $J = 14.0$, 10.3, 6.7 Hz, 1H), 1.55 (ddd, $J = 14.0$, 10.9, 6.3 Hz, 1H), 1.38–1.19 (m, 2H), 1.18–0.99 (m, 2H), 0.86 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.9$, 150.4, 143.2, 142.3, 129.0, 124.5, 111.6, 61.1, 51.9, 51.1, 32.7, 26.7, 23.1, 13.8 ppm; HRMS (ESI): *m/z*: calcd for $C_{16}H_{21}N_2O_5S$: 353.1166 $[M+H]^+$; found: 353.1171; CSP-HPLC (IC, *n*-hexane/*i*PrOH 20:80, 1 mL min^{-1}, 215 nm): *er* = 73.5:26.5; t_R(minor) = 17.89 min, t_R(major) = 20.94 min; $[\alpha]_D^{20} = +47.5$ ($c = 1$ in $CHCl_3$).

1-(Mesitylsulfonyl)-3-methyl-4-methylenepyrrolidine-3-carbaldehyde (**6i**): Prepared according to the above general protocol starting from **5i** (61.4 mg, 0.20 mmol) at 20 °C for 3 days. Colorless solid (54.0 mg, 88% yield); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.31$ (s, 1H), 6.96 (s, 2H), 5.25 (s, 1H), 5.07 (s, 1H), 4.05–3.95 (m, 1H), 3.92–3.82 (m, 1H), 3.76 (d, $J = 9.8$ Hz, 1H), 3.14 (d, $J = 9.8$ Hz, 1H), 2.62 (s, 6H), 2.30 (s, 3H), 1.26 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.7$, 145.7, 143.2, 140.7, 132.1, 131.5, 110.8, 57.1, 52.6, 50.9, 22.9, 21.1, 18.6 ppm; HRMS (ESI): *m/z*: calcd for $C_{16}H_{22}NO_3S$: 308.1315 $[M+H]^+$; found: 308.1320; CSP-HPLC (IC, *n*-hexane/*i*PrOH 70:30, 1 mL min^{-1}, 215 nm): *er* = 85.5:14.5; t_R(minor) = 24.44 min, t_R(major) = 27.25 min; $[\alpha]_D^{20} = +41.5$ ($c = 1$ in $CHCl_3$).

3-Methyl-4-methylene-1-(2,4,6-tri**iso**propylphenylsulfonyl)pyrrolidine-3-carbaldehyde (**6j**): Prepared according to the above general protocol starting from **5j** (75.2 mg, 0.20 mmol) at 20 °C for 4 days. Colorless solid (61.0 mg, 81% yield); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 9.37 (s, 1H), 7.17 (s, 2H), 5.25 (s, 1H), 5.06 (t, $J = 2.0$ Hz, 1H), 4.18 (hept, $J = 6.7$ Hz, 2H), 4.00 (dt, $J = 13.7$, 2.0 Hz, 1H), 3.94–3.80 (m, 2H), 3.20 (d, $J = 9.8$ Hz, 1H), 3.02–2.80 (m, 1H), 1.33–1.20 ppm (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.8$, 153.7, 151.8, 145.9, 130.1, 124.1, 110.8, 56.9, 52.7, 51.3, 34.3, 29.6, 25.1, 25.0, 23.7, 19.0 ppm; HRMS (ESI): *m/z*: calcd for $C_{22}H_{34}NO_3S$: 392.2254 $[M+H]^+$; found: 392.2262; CSP-HPLC (IC, *n*-hexane/*i*PrOH 80:20, 1 mL min^{-1}, 215 nm): *er* = 73:17; t_R(minor) = 8.27 min, t_R(major) = 9.06 min; $[\alpha]_D^{20} = +49.2$ ($c = 1$ in $CHCl_3$).

cis- and *trans*-Methyl 3-formyl-3-methyl-4-methylenecyclopentane-1-carboxylate (**8a**,**b**): Prepared according to the above general protocol starting from **7** (37.0 mg, 0.20 mmol) at 20 °C for 1 day. Colorless oil (32.0 mg, 81% yield) as a 86:14 mixture of **8a/8b**; ^{1}H NMR (300 MHz, $CDCl_3$) **8a**: $\delta = 9.36$ (s, 1H), 5.17 (t, $J = 1.9$ Hz, 1H), 4.85 (dd, $J = 2.7$, 2.0 Hz, 1H), 3.71 (s, 3H), 2.99 (tt, $J = 10.1$, 7.4 Hz, 1H), 2.82–2.60 (m, 2H), 2.47 (dd, $J = 13.1$, 10.1 Hz, 1H), 1.86 (dd, $J = 13.0$, 6.3 Hz, 1H), 1.23 ppm (s, 3H); **8b**: $\delta = 9.26$ (d, $J = 1.1$ Hz, 1H), 5.22 (t, $J = 1.9$ Hz, 1H), 4.96 (t, $J = 2.3$ Hz, 1H), 3.70 (s, 3H), 2.93–2.81 (m, 1H), 2.76–2.64 (m, 2H), 2.59 (dd, $J = 12.9$, 7.0 Hz, 1H), 1.85–1.70 (m, 1H), 1.29 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) **8a**: $\delta = 200.0$, 174.7, 151.4, 110.1, 57.1, 51.8, 41.5, 37.8, 37.0, 21.4 ppm; **8b**: $\delta =$ 199.6, 175.0, 150.4, 110.1, 57.3, 51.7, 40.8, 37.0, 36.4, 20.7 ppm; HRMS (ESI): *m/z*: calcd for $C_{10}H_{14}O_3Na$: 205.0835 $[M+Na]^+$; found: 205.0837; CSP-HPLC **8a**: (IC, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er* = 57:43; t_R(minor) = 11.43 min, t_R(major) = 13.52 min, **8b**: (ID, *n*-hexane/*i*PrOH 90:10, 1 mL min^{-1}, 215 nm): *er* = 92.5:7.5; t_R(minor) = 7.02 min, t_R(major) = 7.41 min.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique and the Ministère de l'Enseignement Supérieur et de la Recherche (MESR) for financial support. B.M. is grateful to MESR for a grant (2009–2012), and C.P. is grateful to Ville de Paris for a postdoctoral fellowship. The authors thank Dr. M. Scalone (Hoffmann-La Roche) for generous gift of 4-MeO-3,5-(tBu)$_2$-MeOBIPHEP ligand.

Keywords: aldehydes · alkynes · asymmetric catalysis · metal catalysis · organocatalysis

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Received: April 25, 2013
Revised: June 4, 2013
Published online on ■■ ■■, 0000