Organic & Biomolecular Chemistry

Accepted Manuscript

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Organic & Biomolecular Chemistry

PAPER

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

The Asymmetric Cu(II)-Indolinylmethanol Complex Catalyzed Diels-Alder Reaction of 2-Vinylindoles with β,γ-Unsaturated α-Ketoesters: An Efficient Route to Functionalized Tetrahydrocarbazoles

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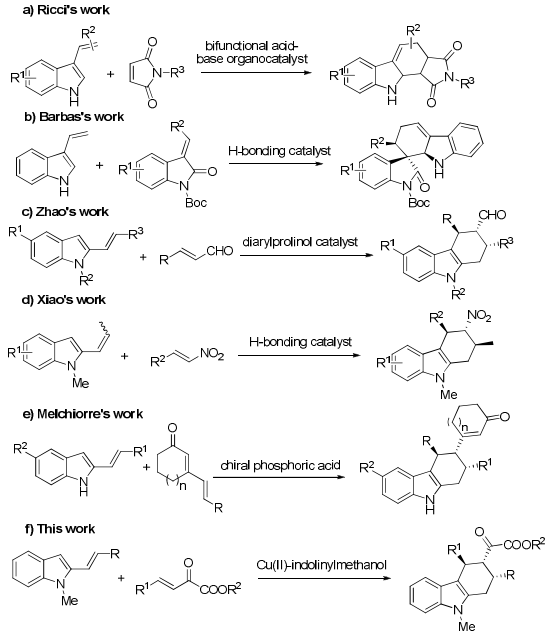
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

An efficient asymmetric Diels-Alder reaction of 2-vinylindoles with β,γ-unsaturated α-ketoesters has been developed for the construction of functionalized tetrahydrocarbazoles. The products were obtained in high yields (up to 96%) with good stereoselectivities (*ee* up to 95%, *dr* up to >99:1).

Introduction

Tetrahydrocarbazole scaffold is present in many naturally occurring and artificial biologically active compounds.[1] Although many asymmetric methods have been developed to access this chiral cyclic architectures,[2] the catalytic stereoselective Diels-Alder reaction is synthetically more efficient. When using 2-vinylindoles or 3-vinylindoles as diene counterparts, various dienophiles (maleimides, methyleneindolinones, nitroolefins or α,β-unsaturated aldehydes *etc.*) can be used to construct the tetrahydrocarbazole scaffold, up to four stereogenic centers can be established simultaneously (Scheme 1).[3] For example, Ricci *et al.* developed a catalytic asymmetric Diels-Alder reaction of 3-vinylindoles with maleimides and quinines, and achieved high yields and excellent enantioselectivities in the presence of bifunctional acid-base organocatalyst.[3b] Later Barbas's group described a highly efficient organocatalytic Diels-Alder reaction of 3-vinylindoles with methyleneindolinones for the direct synthesis of carbazolespirooxindole derivatives in almost quantitative yields with excellent stereoselectivities.[3c] Zhao *et al.* have realized enantio- and diastereoselective Diels-Alder reaction between 2-vinylindoles and α,β-unsaturated aldehydes.[3d] Xiao and coworkers provided an efficient access to a variety of multisubstituted tetrahydrocarbazoles with high stereoselectivities via the reaction of 2-propenylindoles with nitroolefins.[3e]

Recently, Melchiorre *et al.* developed a highly stereo- and regioselective vinylogous Diels-Alder reaction of 2-vinylindoles with cyclic dienones for the synthesis of structurally diverse tetrahydrocarbazoles.[3f] MacMillan's group described the tandem Diels-Alder reactions of 2-vinyltryptamines, which were successfully applied in the total synthesis of some naturally biological active compounds such as (-)-Minfiensine, (-)-Vincorine and (-)-Minovincine respectively.[3g-i] Despite these contributions, the development of direct Diels-Alder reaction of 2-vinylindoles or 3-vinylindoles with β,γ-unsaturated α-ketoester dienophiles is still a challenging frontier in asymmetric catalysis



Scheme 1 Diels-Alder reactions of 2 or 3-vinylindoles

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Electronic Supplementary Information (ESI) available: [Experimental procedures, analytical and spectroscopic data for synthetic compounds, copies of NMR spectra and HPLC chromatograms, crystallographic data in CIF for CCDC 978574]. See DOI: 10.1039/b000000x/

field.

Chiral indole derivatives have recently been successfully utilized in a variety of asymmetric reactions, such as nucleophilic addition of diethylzinc to aldehydes, ketone reduction, aldol reactions and so on.[4] Our group has also developed some novel dihydroindole and perhydroindole derivatives for the asymmetric Michael reaction of aldehydes to nitroalkenes[4a] and Reformatsky reactions.[4h] Compared with their parent pyrrolidine analogs, indole derivatives possessing an additional cyclohexane or phenyl rings in the molecular skeletons, may exert stronger influences on the orientation of substrates, hence improving the stereoselectivity for the asymmetric reaction.

We were interested in accessing new structurally diverse tetrahydrocarbazole systems as drug candidates. Herein we have developed the catalytic asymmetric Diels-Alder reaction of 2-vinylindoles with β,γ-unsaturated α-ketoesters, which has not been reported in literatures (Scheme 1e). Using chiral Cu(II)-indolinylmethanol complex as catalyst, the corresponding cycloadducts were obtained in high yields (up to 96%) with good stereoselectivities (*ee* up to 95%, *dr* up to >99:1).

Results and discussions

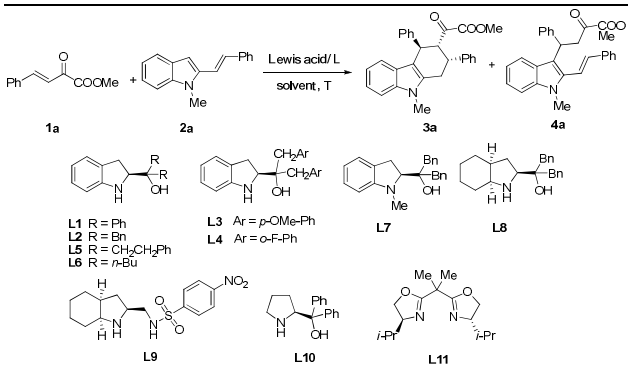
Chiral copper salts possess proper Lewis acidities and electrophilic activities, and have been successfully utilized in many enantioselective Diels-Alder reactions.[5] So we chose chiral copper salts as Lewis acids for the cycloaddition reaction. β,γ-Unsaturated α-ketoester **1a** and 2-vinylindole **2a** were used as dienophile and diene respectively, the ketoester moiety of **1a** was anticipated to have strong chelation with chiral copper catalyst, hence inducing good stereoselectivities (both *ee* and *dr*) for the model reaction.

In the absence of any copper catalyst, the reaction between **1a** and **2a** at room temperature afforded both [4+2] adduct **3a** and Friedel-Crafts alkylation product **4a** in 76% and 11% yield respectively (Table 1 entry 1). But in the presence of $Cu(OTf)_2$, the Friedel-Crafts alkylation was totally inhibited, only cycloadduct **3a** could be isolated in 88% yield and 92:8 *dr* (Table 1 entry 2). The combination of $Cu(OTf)_2$ and chiral indolinylmethanol **L2** gave the desired cycloadduct in high yield with good enantioselectivity (82% *ee*, Table 1 entry 4). Encouraged by these preliminary results, we further examined the effects of temperatures, Lewis acids, chiral ligands and solvents on both the yields and the stereoselectivities.

The reaction temperatures showed slight influences on the reaction selectivity, albeit 30 °C resulted in higher ee (Table 1 entry 5). Higher or lower temperatures than 30 °C caused decreases in enantioselectivities (Table 1, entries 3-6). Various Lewis acids were screened and $Cu(OTf)_2$ was found to be the optimal choice for the Diels-Alder reaction. $Zn(OTf)_2$ led to similar yield and diastereoselectivity, but significantly lower ee values than $Cu(OTf)_2$ (Table 1, entry 10). Other Lewis acids as $Sc(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$ and $Cu(OAc)_2$•H_2O all provided poor asymmetric inductions (Table 1, entries 7-9, 11).

Subsequently, various chiral ligands were evaluated. Chiral indolinylmethanol ligands **L1-L6** exhibited moderate to good levels of asymmetric inductions, depending on the steric nature of substituents on the indolinylmethanols. For example, ligand **L1** with phenyl substituent furnished the product with good diastereoselectivity but poor enantioselectivity (Table 1, entry 12).

Table 1 Optimization of the reaction conditions[a]



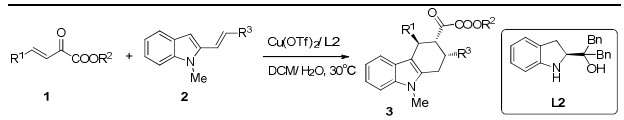
Entry	T (℃)	L	Lewis acid	Solvent	Yield[b] (%)	*dr*[c]	*ee*[d] (%)
1	rt	/	/	DCM	76	79:21	0
2	rt	/	$Cu(OTf)_2$	DCM	88	92:8	0
3	0	**L2**	$Cu(OTf)_2$	DCM	84	79:21	74
4	rt	**L2**	$Cu(OTf)_2$	DCM	91	87:13	82
5	30	**L2**	$Cu(OTf)_2$	DCM	90	86:14	90
6	40	**L2**	$Cu(OTf)_2$	DCM	82	84:16	86
7	30	**L2**	$Sc(OTf)_3$	DCM	86	69:31	1
8	30	**L2**	$Yb(OTf)_3$	DCM	76	73:27	8
9	30	**L2**	$In(OTf)_3$	DCM	53	81:19	6
10	30	**L2**	$Zn(OTf)_2$	DCM	91	82:18	51
11	30	**L2**	$Cu(OAc)_2$•H_2O	DCM	40	73:29	5
12	30	**L1**	$Cu(OTf)_2$	DCM	71	93:7	48
13	30	**L3**	$Cu(OTf)_2$	DCM	92	86:14	82
14	30	**L4**	$Cu(OTf)_2$	DCM	97	85:15	90
15	30	**L5**	$Cu(OTf)_2$	DCM	87	86:14	70
16	30	**L6**	$Cu(OTf)_2$	DCM	75	88:12	55
17	30	**L7**	$Cu(OTf)_2$	DCM	60	85:15	0
18	30	**L8**	$Cu(OTf)_2$	DCM	50	90:10	1
19	30	**L9**	$Cu(OTf)_2$	DCM	86	87:13	0
20	30	**L10**	$Cu(OTf)_2$	DCM	48	89:11	0
21	30	**L11**	$Cu(OTf)_2$	DCM	69	79:21	10
22	30	**L2**	$Cu(OTf)_2$	toluene	88	79:21	84
23	30	**L2**	$Cu(OTf)_2$	DCE	95	85:15	77
24	30	**L2**	$Cu(OTf)_2$	$CHCl_3$	95	80:20	80
25	30	**L2**	$Cu(OTf)_2$	DCM[e]	90	92:8	95
26	30	**L2**	$Cu(OTf)_2$	DCM[f]	76	85:15	75
27[g]	30	**L2**	$Cu(OTf)_2$	DCM	77	84:16	75

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Lewis acid (10 mol%), ligand (10 mol%), 1.5 mL solvent. [b] Isolated yield of **3a**. [c] Determined by chiral HPLC analysis and NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis. [e] 0.1 mmol H_2O was added to 1.5 mL DCM. [f] DCM was saturated with H_2O. [g] 5 mol% $Cu(OTf)_2$ and 5 mol% **L2** were used.

Indolinylmethanols **L2-L4** with benzylic or substituted benzylic substituents gave **3a** in good yields and high *ee* values (Table 1, entries 5 and 13-14), and **L2** was the best ligand. Further increasing the length of the carbon chain of the substituents on the indolinylmethanols led to worse results (Table 1, entries 15-16). *N*-protected indolinylmethanol **L7**, perhydroindole derivatives **L8** and **L9**, proline-derived amino alcohol **L10** proved to be completely unselective (Table 1, entries 17-20). Although chiral bisoxazoline **L11** has been widely used in many catalytic asymmetric reactions[5c,6], it only provided poor enantioselectivity in this Diels-Alder reaction (Table 1, entry 21). A survey of reaction media revealed that CH_2Cl_2 was the optimal solvent (Table 1, entry 5 vs entries 22-24). Interestingly, the

content of H_2O in CH_2Cl_2 was quite important for good stereoselectivity, the existence of 0.1 mmol H_2O in catalytic system led to improved diastereoselectivity and enantioselectivity (92:8 *dr* and 95% *ee*), while H_2O-saturated CH_2Cl_2 as solvent furnished the cycloadduct in 76% yield with 75% *ee* (Table 1, entry 5 and entries 25-26). Reducing the loading of $Cu(OTf)_2$/**L2** to 5 mol% caused significant loss in ee and yield (Table 1, entry 27).

Table 2 Scope of the reaction[a]



Entry	R^1	R^2	R^3	**3**	Yield[b] (%)	*dr*[c]	*ee*[d] (%)
1	Ph	Me	Ph	**3a**	90	92:8	95
2	Ph	Et	Ph	**3b**	89	87:13	53
3	Ph	*i*-Pr	Ph	**3c**	95	91:9	34
4	*o*-F-Ph	Me	Ph	**3d**	96	>99:1	93
5	*m*-F-Ph	Me	Ph	**3e**	94	84:16	50
6	*p*-F-Ph	Me	Ph	**3f**	86	94:6	52
7	*o*-Cl-Ph	Me	Ph	**3g**	91	89:11	67
8	*p*-Cl-Ph	Me	Ph	**3h**	84	99:1	56
9	*o*-Br-Ph	Me	Ph	**3i**	80	93:7	71
10	*p*-Me-Ph	Me	Ph	**3j**	77	94:6	59
11	*p*-Ph-Ph	Me	Ph	**3k**	68	95:5	57
12	*o*-MeO-Ph	Me	Ph	**3l**	80	94:6	87
13	*m*-MeO-Ph	Me	Ph	**3m**	84	88:12	58
14	*p*-MeO-Ph	Me	Ph	**3n**	86	90:10	78
15	2,5-$(MeO)_2$-Ph	Me	Ph	**3o**	84	93:7	91
16		Me	Ph	**3p**	86	98:2	42
17	Ph	Me	*p*-Br-Ph	**3q**	82	99:1	59
18	*o*-F-Ph	Me	*p*-Br-Ph	**3r**	79	99:1	56
19	2,5-$(MeO)_2$-Ph	Me	*p*-Br-Ph	**3s**	82	99:1	68
20	*o*-MeO-Ph	Me	*p*-Br-Ph	**3t**	69	99:1	90
21	Ph	Me	*p*-Me-Ph	**3u**	73	99:1	56
22	*o*-MeO-Ph	Me	*p*-Me-Ph	**3v**	91	96:4	50

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), $Cu(OTf)_2$ (10 mol%), **L2** (10 mol%), DCM (1.5 mL), H_2O (0.1 mmol), 30 □. [b] Isolated yield. [c] Determined by chiral HPLC analysis and NMR spectroscopic analysis. [d] Determined by chiral HPLC analysis.

With the established conditions in hand, we next examined the scope and limitations of both β,γ-unsaturated α-ketoester and 2-vinylindole substrates. The results were summarized in Table 2. Changing the ester moiety of β,γ-unsaturated α-ketoesters **1** from COOMe to more hindered COOEt or COO*i*Pr did not affect the reactivity and diastereoselectivity, but the *ee* values dramatically decreased to 53% and 34% respectively (Table 2, entries 1-3). A variety of aromatic β,γ-unsaturated α-ketoesters could be used in this reaction, giving the corresponding products **3** in good yields with high *dr* values and moderate to high *ee* values (Table 2,entries 4-15). The steric hindrance of R^1 substituent on **1** showed significant influences on the enantioselectivities, when R^1 was an *ortho*-substituted phenyl group, higher ees were achieved (Table 2, entry 4 vs entries 5 and 6, entry 12 vs entries 13 and 14). Smaller 2-fluorophenyl substituted **1** afforded product **3d** in 96% yield with 93% ee (Table 2, entry 4), while larger 2-bromophenyl substituted **1** provided **3i** in 80% yield with 71% ee (Table 2, entry 9), we attributed this to the proper steric hindrance of 2-fluoro substituent. The reaction was also sensitive to the electronic properties of the β,γ-unsaturated α-ketoester. 4-Methoxyphenyl substituted substrate **1** yielded the corresponding product in good enantioselectivity (Table 2, entry 14), while 4-fluorophenyl substituted β,γ-unsaturated α-ketoester gave the cycloadduct with only 52% ee (Table 2, entry 6). Heteroaryl substituted **1** was also suitable for this cycloaddition reaction, desired product **3p** can be isolated in good yield and high diastereoselectivity, albeit its enantioselectivity was moderate (Table 2, entry 16).

We also expanded our catalytic system to other 2-vinylindoles. Preliminary studies showed that good yields, high *dr* values and moderate to high *ee* values were generally obtained for the desired products **3** (Table 2, entries 17-22). The absolute configuration of **3a** was unambiguously determined to be (2*R*,3*R*,4*R*) by X-ray crystallographic analysis (Fig. 1). The configurations of other products were determined by analogy to **3a**.

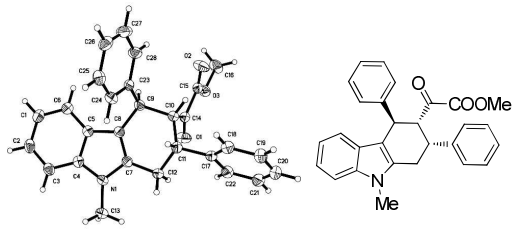


Fig. 1 The X-ray crystal structure of enantiomerically pure **3a**

Based on previous studies[5,7] and the crystal structure of product **3a**, we speculated that a concerted mechanism was more convincing. A possible transition-state stereomodel with a distorted octahedral geometry at the copper centre was proposed to account for the stereoselectivity of this Diels–Alder reaction (Fig. 2). The 2-vinylindole attacked the β,γ-unsaturated α-ketoester preferably from the underside via an *endo*-approach, leading to the formation of the predominant (2*R*,3*R*,4*R*)-product. Benzylic chain of the ligand induced a better selectivity for it might cover partial face of the ketoester. Water is crucial for high ee, we attributed this to its coordination with copper,[7] which might modify the geometry of copper centre and enhance the stereofacial selection.

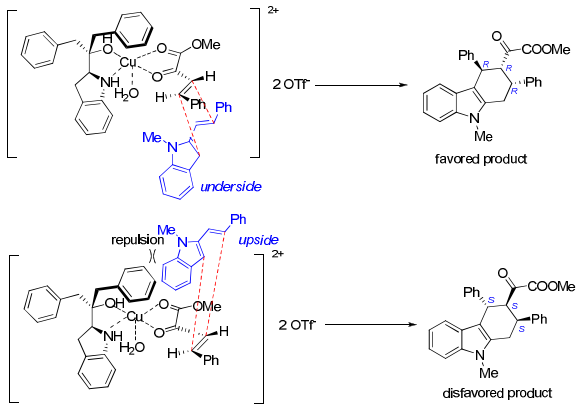


Fig. 2 Proposed transition state for the Diels-Alder reaction

Conclusions

In conclusion, we have developed an efficient asymmetric Diels-Alder reaction of 2-vinylindoles with β,γ-unsaturated α-

ketoesters. With chiral $Cu(OTf)_2$/indolinylmethanol complex as catalyst, highly functionalized tetrahydrocarbazoles can be achieved straightforwardly in high yields (up to 96%) with moderate to good stereoselectivities (up to >99:1 *dr*, up to 95% *ee*). Further application of this method for the synthesis of structurally diverse tetrahydrocarbazole system as drug candidates is currently underway in our laboratory.

Acknowledgements

This work was financially supported by the National High-tech R&D Program of China (863 Program, No. 2013AA092903) and Guangdong Innovative Research Team Program (No. 2009010058).

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