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An efficient synthesis of indane-derived bis(oxazoline) and its application to hetero Diels–Alder reactions on polymer support

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Abstract—Indane-derived bis(oxazolines) were synthesized in two steps and 93% overall yield starting from commercially available substrates. This ligand is as effective as *tert*-butyl bis(oxazoline) in hetero Diels–Alder reaction both in solution and on polymer support.

Since the introduction of C_2-symmetric chiral bis(oxazoline) (Box) ligands in copper-catalyzed asymmetric cyclopropanations by Masamune in 1990,[1] these compounds have been of considerable interest as versatile bidentate (or tridentate) ligands in asymmetric reactions.[2] A variety of Box ligands have been designed and applied to stoichiometric and catalytic asymmetric reactions.[3] Evans and co-workers have reported that (*S*,*S*)-*tert*-butylbis(oxazoline) ((*S*,*S*)-*t*-Bu-Box) (**1**) derived from (*S*)-*tert*-leucine is the optimal ligand for a number of asymmetric transformations such as Mukaiyama aldol reaction, Mukaiyama–Michael reaction, Diels–Alder cycloaddition, and cyclopropanation (Fig. 1).[4] However, *t*-Bu-Box ligands are composed of expensive building blocks[5] and their synthesis requires purification by chromatography.[6] The Box ligand derived from optically pure *cis*-1-amino-2-indanol (Inda-Box) (**2**) has been utilized in a few asymmetric transformations such as a Diels–Alder reaction[7] and conjugate addition of 1,3-dicarbonyl compounds.[8]

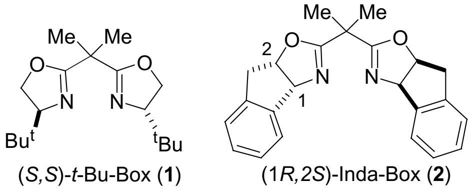

Figure 1.

In an effort to synthesize a large collection of diverse and complex molecules efficiently, we became interested in reagent-controlled asymmetric reactions on polymer-supported molecules. Schreiber and Stavenger have demonstrated Cu-(*S,S*)-*t*-Bu-Box (**1**) and Cu-*ent*-**1** catalyzed hetero Diels–Alder reactions[9] for the construction of a 4232-member dihydropyrancarboxamide library made on 500 μm polystyrene beads.[10] We now wish to report a very practical synthesis of optically pure Inda-Box ligand **2** in two steps with 93% overall yield after a single crystallization and its application to asymmetric hetero Diels–Alder reactions on a polymer support.

Inda-Box (**2**) is commonly synthesized via condensation of ethyl 3-amino-3-ethoxyprop-2-enimidate and 1-amino-2-indanol (**3**), followed by double alkylation of **4** under anhydrous conditions (path a in Scheme 1).[2,11] Although effective on a small scale, these sequences suffer from low overall yield. Therefore we investigated a more convenient method for this transformation. After acylation of **3** with dimethylmalonyl chloride to give diamide **5**, we investigated a higher yielding method for cyclization of **5** to oxazoline **2**. Since Bu_2SnCl_2[1b] and BF_3–OEt_2[12] at elevated temperature are known to catalyze oxazoline formation with retention of secondary alcohol stereochemistry, we applied these conditions for the synthesis of Inda-Box **2**. Unfortunately, these conditions resulted in poor conversion of **5** to cyclized product **2**

Keywords: bis(oxazoline); hetero Diels–Alder reaction; polymer support; dihydropyrancarboxylic acid; diversity-orientated synthesis.

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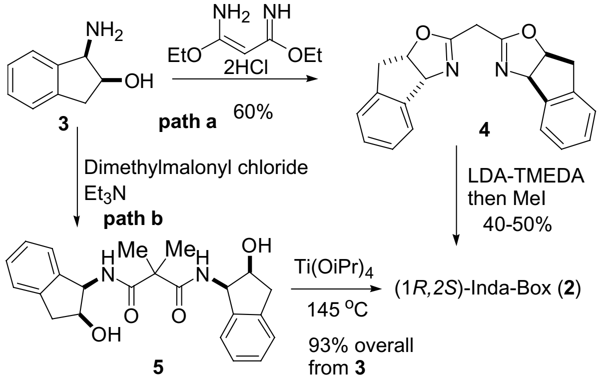
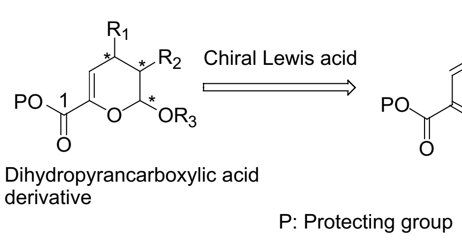


Scheme 1.

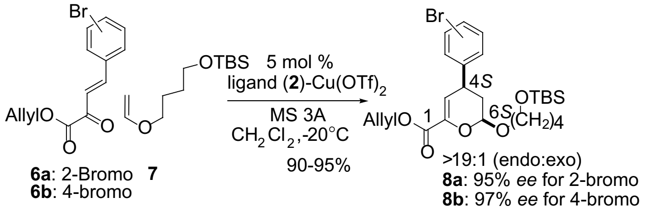
(e.g., 10–15% conversion with Bu_2SnCl_2 at 140 °C). Gratifyingly, we found that Ti(O^{i}Pr)$_4$ facilitates the transformation of **5** to **2** at 140–145 °C in very high yield (path b). To further improve this protocol, we developed an efficient method to remove Ti(O^{i}Pr)$_4$ and other Ti species from the reaction mixture. Ti species are solubilized and extracted from the organic solution by complexation with 3-(dimethylamino)-1,2-propanediol.[13] Crystallization from acetonitrile affords Inda-Box **2** in 93% overall yield from **3**. The synthesis of each enantiomer was performed on a 100 g scale.

As mentioned above, the utility of Box–metal complexes in solution-phase asymmetric reactions (target-oriented synthesis) has been demonstrated by a number of groups. However, its application in diversity-oriented synthesis,[14] which is generally performed on polymer support is less developed. We have been interested in dihydropyrancarboxylic acid derivative (Scheme 2) as a skeleton for small drug-like molecules. Evans and coworkers have demonstrated that [Cu(*S*,*S*)-*t*-Bu-Box (**1**)](OTf)$_2$ catalyzed asymmetric hetero Diels–Alder reactions (inverse electron demand heterocycloadditions of vinyl ethers and unsaturated ketoesters) generates a dihydropyran core with up to three chiral centers in a single operation (Scheme 2).[9]



Scheme 2.

Toward the construction of dihydropyrancarboxylic acid derivatives possessing 4*S* and 6*S* stereochemistries, we examined the hetero Diels–Alder reactions in solution using (1*R*,2*S*)-Inda-Box (**2**) and Cu(OTf)$_2$. More than 10 different heterodienes were tested and representative examples are summarized in Scheme 3. The reaction of **6a** and **6b** with **7** (5 mol% catalyst) afforded the desired allyl dihydropyrancarboxylates **8a** and **8b** in >90% yield with >19:1 diastereoselectivity and 95% ee. These experiments demonstrate that *t*-Bu-Box ligand can be replaced with Inda-Box (**2** and its enantiomer) in the hetero Diels–Alder reaction.



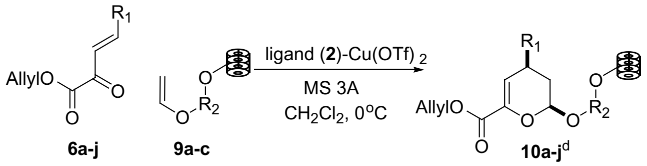
Scheme 3.

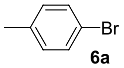
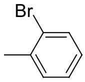
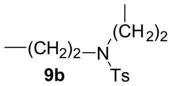
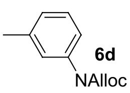
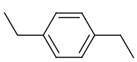
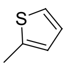
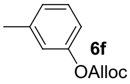
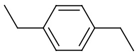
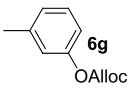
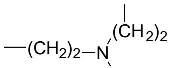
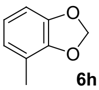
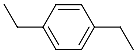
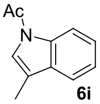
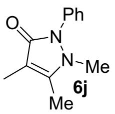
In order to investigate the applicability of the (Inda-Box)–Cu(OTf)$_2$ catalyst to polymer-supported vinyl ethers, three different vinyl ethers were loaded onto the Lantern^{TM}.[15] The polymer-supported vinyl ethers were subjected to hetero Diels–Alder reactions with structurally diverse heterodienes (**6a**–**j**) using 100 mol% of [(1*R*,2*S*)-Inda-Box–Cu(OTf)$_2$]. Desired allyl dihydropyrancarboxylates (**8a**–**j**) were isolated with good diastereoselectivities and 86–97% ee as summarized in Table 1. These results clearly indicate that [Inda-Box–Cu(OTf)$_2$] catalyst tolerates a variety of heterodienes and vinyl ethers as well as solid phase asymmetric synthesis.

In summary, we have developed an efficient synthetic method for the preparation of Inda-Box (**2**) and shown that the Inda-Box–Cu(OTf)$_2$ complex catalyzes hetero Diels–Alder reactions with polymer-supported vinyl ethers to afford dihydropyrancarboxylic acid derivatives with excellent diastereo- and enantioselectivities. Other asymmetric reactions on the polymer support promoted by Inda-Box–metal complex are currently under investigation.[16]

Procedure for the synthesis of (1*R*,2*S*)-*Inda-Box* (**2**). To a stirred solution of (1*R*,2*S*)-1-amino-2-indanol (90 g, 0.604 mol) in CH_2Cl_2 (1 L) was added triethylamine (336 mL, 2.56 mol, 4 equiv). At 0 °C, a solution of dimethylmalonyl chloride (42.4 mL, 0302 mol, 0.5 equiv) in CH_2Cl_2 (150 mL) was added slowly via a dropping funnel. The reaction mixture was stirred at 0 °C for 2 h and warmed to ambient temperature. After being stirred for 6 h, the reaction mixture was acidified with 1 N HCl. The water phase was extracted with CH_2Cl_2. The combined organic extracts were washed with aq $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated in vacuo to give a crude mixture. Ti(O^{i}Pr)$_4$ (97%, 712 mL, 2.42 mol, 4 equiv) was added into the crude dihydroxy malonodiamide **5** and the reaction mixture was stirred for 145 °C for 8 h while ^{i}PrOH was removed via a Dean–Stark trap during the reaction. The reaction was cooled to ambient temperature and 3-(dimethylamino)-1,2-propanediol (344 mL, 2.90 mol, 1.2 equiv to Ti) was added. After 30 min, EtOAc (1 L) and water (1 L) were added and the reaction mixture was stirred for an additional 30–60 min (the white suspension became com-

Table 1. Hetero Diels–Alder reaction with polymer-supported vinyl ethers[a]



Entry	R_1	R_2	Endo/exo[b]	Ee (%)[c]
1	 **6a**	$-(CH_2)_4-$ **9a**	12:1	95
2	 **6b**	$-(CH_2)_4-$ **9a**	13:1	95
3	 **6c**	 **9b**	12:1	90
4	 **6d**	 **9c**	15:1	87
5	 **6e**	$-(CH_2)_4-$ **7a**	12:1	85
6	 **6f**	 **9c**	14:1	98
7	 **6g**	 **9b**	10:1	86
8	 **6h**	 **9c**	10:1	95
9	 **6i**	$-(CH_2)_4-$ **9a**	12:1	86
10	 **6j**	$-(CH_2)_4-$ **9a**	10:1	98

[a] All reactions were carried out using 100 mol% of (1*R*,2*S*)-Inda-Box (**2**) and $Cu(OTf)_2$ for 12 h. De and ee were determined with alcohols after cleaving from polymer support.

[b] De was determined by ^1H NMR.

[c] Ee was established by chiral HPLC.

[d] The absolute chemistry of the products was assigned by chemical correlation with reported stereochemistry.[9]

pletely soluble). The water phase was extracted with EtOAc and the combined extracts were dried over Na_2SO_4, and concentrated in vacuo to give crude **2**. This was recrystallized from CH_3CN (twice) to give **2** as a fine white powder (100 g, 93%). $[\alpha]_D$ +430 (*c* 0.6, $CHCl_3$, 23 °C).

General procedure for hetero Diels–Alder reactions on polymer-supported vinyl ethers. One lantern (20–30 μmol), heterodiene (1.2 equiv), and MS 3A (50 mg) were placed in a flask and CH_2Cl_2 (1 mL) was added. The reaction mixture was agitated for 30 min at ambient temperature and then cooled to −78 °C. A 1:1 mixture of

(1*R*,2*S*)-Inda-Box (**2**) and $Cu(OTf)_2$ generated in another flask (0.1 M in CH_2Cl_2, 0.2–0.3 mL) was added to the reaction mixture. This mixture was allowed to cool to 0 °C and shaken for 12 h. The lantern was washed with THF, THF–water (3:1), THF, and EtOAc. The dihydropyrancarboxylate was cleaved from the lantern under a buffered HF–pyridine (70% HF–pyridine/pyridine/THF = 1:1:1, 0.6 mL) for 1.5 h and quenched with TMSOMe (1.2 mL) for 30 min. Diastereo- and enatioselectivities of the product were determined by ^{1}H NMR and chiral HPLC (Chiralcel OD and Chiralcel OJ), respectively (see Table 1).

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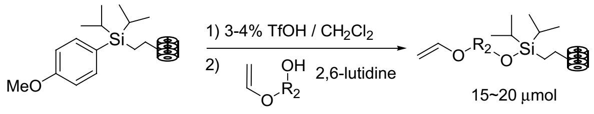
15. (a) Lantern^{TM} (trademark of Mimotopes Pty, Ltd) is cylindrical in appearance and a polystyrene grafted surface. We utilized L-series lanters (height: 5 mm, diameter: 5 mm, surface area: 1.7 cm^2). The general loading for this type of L-series lantern is 15–20 μmol; for more information, see http://www.mimotopes.com; (b) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, *3*, 312–318,



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16. Inda-Box would be applied to many other asymmetric reactions as a replacement of *t*-Bu-Box ligand because of its conformationally constrained structure, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.