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Enantioselective Synthesis of Indole-Fused Dihydropyranones via Catalytic Cycloaddition of Ketenes and 3-Alkylenyloxindoles

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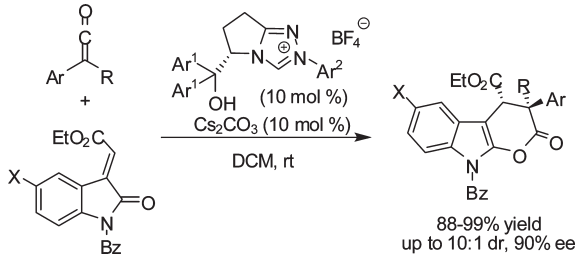

Chiral N-heterocyclic carbenes were found to be efficient catalysts for the formal [4+2] cycloaddition reaction of alkyl(aryl)ketenes and 3-alkylenyloxindoles to give the corresponding 3,4-dihydropyrano[2,3-*b*]indol-2-ones in excellent yields with good diastereo- and enantioselectivities.

Convenient methods for constructing molecules with two separate biologically interesting scaffolds that are fused are of great value for both organic and medicinal chemists.[1] The indole ring is regarded as a privileged structure in many biologically active natural products and pharmaceutical agents.[2] Consequently, great efforts have been devoted to the synthesis of various fused indoles, and many efficient approaches have been documented.[3] In the meantime, dihydropyranones also present a wide range of biologically active compounds.[4] Thus a hybrid of these two motifs could potentially lead to a series of structurally and biologically interesting compounds (Figure 1). Although the synthesis and application of indole-fused pyranones and their derivatives have been reported sporadically,[5] to the best of our knowledge, the direct asymmetric synthesis of these compounds remains a challenge.

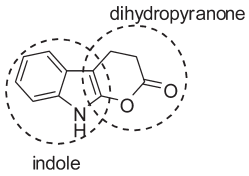

FIGURE 1. Indole-fused dihydropyranones.

N-Heterocyclic carbenes (NHCs) are useful reagents for synthesis of heterocyclic compounds,[6] excellent ligands for organometallic catalysts,[7] and versatile organocatalysts for varied reactions.[8,9] In this context, we, simultaneously with

(1) (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (b) Gil, C.; Brase, S. *J. Comb. Chem.* **2009**, *11*, 175.

(2) For reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Saki, N.; Annaka, K.; Fujita, A.; Sato, A. *J. Org. Chem.* **2008**, *73*, 4160. (e) Bandini, M.; Eichholzer, A. *Angew. Chem. In. Ed.* **2009**, *48*, 9608.

(3) For examples, see: (a) Pudlo, M.; Csanyi, D.; Moreau, F.; Riedl, Z.; Sapi, J. *Tetrahedron* **2007**, *63*, 10320. (b) Majumdar, K. C.; Taher, A.; Ponra, S. *Tetrahedron Lett.* **2010**, *51*, 147. (c) Barluenga, J.; Tudela, E.; Ballesteros, A.; Tomas, M. *J. Am. Chem. Soc.* **2009**, *131*, 2096. (d) Singh, V.; Hutait, S.; Biswas, S.; Batra, S. *Eur. J. Org. Chem.* **2010**, 531. (e) John, J.; Indu, U.; Suresh, E.; Radhakrishnan, K. V. *J. Am. Chem. Soc.* **2009**, *131*, 5042. (f) Fillion, E.; Dumas, A. M. *J. Org. Chem.* **2008**, *73*, 2920. (g) Li, G. J.; Wang, E.; Chen, H.; Li, H. F.; Liu, Y. H.; Wang, P. G. *Tetrahedron* **2008**, *64*, 9033. (h) Halim, R.; Scammells, P. G.; Flynn, B. *Org. Lett.* **2008**, *10*, 1967.

(4) (a) Hamilton, H. W.; Tait, B. D.; Gajda, C.; Hagen, S. E.; Ferguson, D.; Lunney, E. A.; Pavlovsky, A.; Tummino., P. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 719. (b) Krishna, P. R.; Srinivas, R. *Tetrahedron: Asymmetry* **2007**, *18*, 2197. (c) Narasimhulu, M.; Krishna, A. S.; Rao, J. R.; Venkateswarlu, Y. *Tetrahedron* **2009**, *15*, 2989. (d) Kasaplar, P.; Yilmazer, O.; Cağir, A. *Bioorg. Med. Chem.* **2009**, *1*, 311. (e) Mohapatra, D. K.; Das, P. P.; Reddy, D. S.; Yadav, J. S. *Tetrahedron Lett.* **2009**, *43*, 5941. (f) Krishna, P. R.; Srinivas, R. *Tetrahedron Lett.* **2007**, *48*, 2013. (g) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Bioorg. Med. Chem. Lett.* **2009**, *22*, 6396.

(5) (a) Bestmann, H. J.; Schmid, G. *Tetrahedron Lett.* **1984**, *25*, 1441. (b) Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles* **1982**, *17*, 377. (c) Amiet, R. G.; Eastwood, F. W.; Rae, I. D. R. *Aust. J. Chem.* **1972**, *25*, 1473. (d) Nakagawa, M.; Sodeoka, M.; Yamaguchi, K.; Hino, T. *Chem. Pharm. Bull.* **1984**, *32*, 1373. (e) Fritz, H.; Losacker, P. *Justus Liebigs Ann. Chem.* **1967**, *709*, 135. (f) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849. (g) Kam, T. S.; Tan, S. J.; Ng, S. W.; Komiyama, K. *Org. Lett.* **2008**, *10*, 3749. Feldman, K. S.; Vidulova, D. B.; Karatjas, A. D. *J. Org. Chem.* **2005**, *70*, 6429. (h) Reh, S.; Bergman, J. *Tetrahedron* **2005**, *61*, 3115.

(6) (a) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (b) Cheng, Y.; Meth-Cohn, O. *Chem. Rev.* **2004**, *104*, 2507. (c) Cheng, Y.; Wang, B.; Wang, X.-R.; Zhang, J.-H.; Fang, D.-C. *J. Org. Chem.* **2009**, *74*, 2357. (d) Cheng, Y.; Peng, J. H.; Li, J. Q. *J. Org. Chem.* **2010**, *75*, 2382. (e) Cheng, Y.; Liu, M.-F; Fang; Lei, X.-M. *Chem.—Eur. J.* **2007**, *13*, 4282. (f) Ding, H. F.; Zhang, Y. P.; Bian, M.; Yao, W. J.; Ma, C. *J. Org. Chem.* **2008**, *73*, 578. (g) Ma, C.; Yang, Y. W. *Org. Lett.* **2005**, *7*, 1343. (h) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665.

(7) (a) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Topics in Organometallic Chemistry, Vol. 28; Springer-Verlag: Berlin, 2007. (b) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, 2006.

(8) For reviews, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534.

(9) (a) Ugai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296. (*Chem. Abstr.* **1951**, *45*, 5148). (b) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3119. (c) Stetter, H.; Schreckenberg, M. *Angew. Chem.* **1973**, *85*, 89. *Angew. Chem., Int. Ed.* **1973**, *12*, 81. (d) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (e) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (f) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518. (g) Fischer, C.; Smith, S. W.; Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 1472. (h) He, L.; Jian, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (i) Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949. (j) Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 1258. (k) Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266. (l) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334. (m) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 2740. (n) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2680. (o) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (p) Biju, A. T.; Wurz, N. E.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 5970. (q) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, 351. (r) Ye, W.; Cai, G.; Zhuang, Z.; Jia, X.; Zhai, H. *Org. Lett.* **2005**, *7*, 3769. (s) Liu, Y. K.; Li, R.; Yue, L.; Li, B. J.; Chen, Y. C.; Wu, Y.; Ding, L. S. *Org. Lett.* **2006**, *8*, 1521. (t) Sun, X. Y.; Ye, S. Q.; Wu, J. *Eur. J. Org. Chem.* **2006**, 4787.

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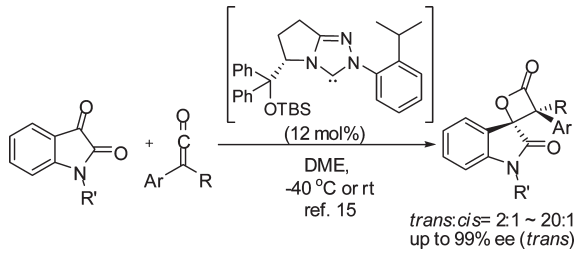
SCHEME 1. NHC-Catalyzed Synthesis of Spirocyclic Oxindole-β-lactones



Smith et al.,[10] demonstrated that NHCs were efficient catalysts for the [2+2] and [4+2] formal cycloaddition of ketenes with imines, enones, etc., to give the corresponding cycloadducts in good yields with excellent enantioselectivties.[11,12] Especially, Bode et al. reported an interesting synthesis of dihydropyranones via the NHC-catalyzed [4+2] cycloaddition reaction of oxodienes and α-chloroaldehydes in 2006.[13] Later, we successfully developed the NHC-catalyzed [4+2] cycloaddition of oxodienes and ketene to give dihydropyranones[14−16] and recently the [2+2] cycloaddition of isatin and ketenes to give spirocyclic oxindole-β-lactones (Scheme 1).[17]

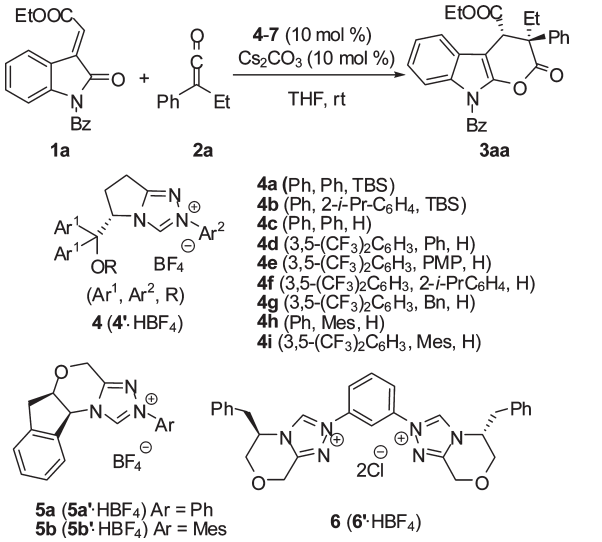
Herein we report an NHC-catalyzed formal cycloaddition of ketenes with alkylenyloxidoles for the direct asymmetric synthesis of indole-fused dihydropyranones. The reaction of phenyl(ethyl)ketene **2a** with 3-alkylenyloxindole **1a** was investigated as the model reaction (Table 1). It was found that NHC **4a′**, generated freshly from the precursor **4** and Cs_2CO_3, could catalyze the reaction of **1a** and **2a** to give the corresponding indole-fused dihydropyranone **3aa** in 61% yield with 2:1 ratio of *trans*/*cis*-isomer and 38% ee for the *trans*-isomer (entry 1).

Then a series of NHC precurors **4b**−**i**,[11,18] derived from L-pyroglutamic acid, were tested as the catalysts. It was found that the reaction catalyzed by NHC **4b′**, with an *N*-2-isopropylphenyl group, gave the product in 78% yield and 40% ee (entry 2).

Recently, we found that the NHCs with a proximal hydroxyl group show a promising enantioselectivity in the aza-Morita−Baylis−Hillman reaction and the dimerization of ketenes.[19] Considering the possible H-bonding between the hydroxyl group of the NHC and the substrate, NHCs with a proximal free hydroxyl group were tested. NHC **4c′**, with a diphenylmethylhydroxyl group, resulted in excellent yield but very low and reversed enantioselectvity (entry 3). In order to increase the H-bond-donating ability of the hydroxyl group, strong electron-withdrawing substituents were introduced into the diarylmethyl group, which led to NHCs **4d′**−**g′**. It was found that the reactions catalyzed by these catalysts gave the desired product in high yields with good enantioselectivities (entries 4−7).

As shown in our previous report, an *N*-bulky group, such as mesityl, also benefits the reversed enantioselectivities,[20] so NHCs **4h′**,**i′**, with an *N*-mesityl group, were tested. While both NHCs **4h′** and **4i′** showed good and reversed ennatioselectivities compared to NHC **4a′**, it is unexpected that no better result was observed for the reaction catalyzed by NHC **4i′**, which bears a better H-bonding donor group than **4h′**

TABLE 1. Screening of N-Heterocyclic Carbenes



entry	cat.[a]	3aa	yield (%)[b]	*trans*:*cis*[c]	ee (%)[d]
1	**4a**	(−)-**3aa**	61	2:1	38
2	**4b**	(−)-**3aa**	78	2:1	40
3	**4c**	(+)-**3aa**	99	4:1	1
4	**4d**	(+)-**3aa**	91	4:1	71
5	**4e**	(+)-**3aa**	98	4:1	54
6	**4f**	(+)-**3aa**	93	3:1	60
7	**4g**	(+)-**3aa**	90	3:1	60
8	**4h**	(+)-**3aa**	95	3:1	66
9	**4i**	(+)-**3aa**	94	3:1	59
10	**5a**	(+)-**3aa**	86	2:1	15
11	**5b**	(−)-**3aa**	73	1:1	12
12	**6**	(+)-**3aa**	67	4:1	13

[a]NHCs **4′**−**6′** were generated from their precursors **4**−**6** (10 mol %) in the presence of Cs_2CO_3 (10 mol %) in the noted solvent at room temperature for 30 min and used immediately. [b]Total yield of the *cis*- and *trans*-isomer. [c]Determined by ^{1}H NMR of the reaction mixture. [d]Determined by chiral HPLC. PMP = *p*-methoxyphenyl, Mes = 2,4,6-trimethylphenyl.

(10) (a) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1108. (b) Concellón, C.; Duguet, N.; Smith, A. D. *Adv. Synth. Catal.* **2009**, *351*, 3001.

(11) (a) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277. (b) He, L.; Lv, H.; Zhang, Y.-R.; Ye, S. *J. Org. Chem.* **200**, *73*, 8101.

(12) For reviews of catalytic reactions of ketenes, see: (a) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545. (b) Tidwell, T. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5778. (c) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563. (d) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771. (e) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(13) (a) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (b) He, M.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817.

(14) Evans et al. reported a copper-catalyzed synthesis of dihydropyrone from silylketene: Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125.

(15) For the pioneering enantioselective [4+2] cycloaddition of ketenes catalyzed by cinchona alkaloid, see: (a) Bekele, T.; Shah, M. H.; Wolfer, J.; Abraham, C. J.; Weatherwax, A.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 1810. (b) Abraham, C. J.; Paull, D. H.; Scerba, M. T.; Grebinski, J. W.; Lectka, T. *J. Am. Chem. Soc.* **2006**, *128*, 13370. (c) Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7398. (d) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951.

(16) (a) Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S. *Chem.—Eur. J.* **2008**, *14*, 8473. (b) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal.* **2009**, *351*, 2822.

(17) Wang, X.-N.; Zhang, Y.-Y.; Ye, S. *Adv. Synth. Catal.* **2010**, *352*, 1892.

(18) (a) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367. (b) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. *J. Org. Chem.* **2009**, *74*, 9214.

(19) (a) He, L.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Synthesis* **2008**, 2825. (b) Lv, H.; Zhang, Y.-R.; Huang, X.-L.; Ye, S. *Adv. Synth. Catal.* **2008**, *350*, 2715.

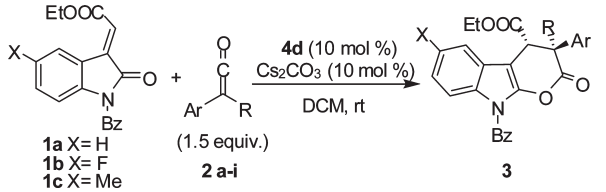
(20) Huang, X.-L.; He, L.; Shao, P.-L.; Ye, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 192.

TABLE 2. Optimization of the Reaction Conditions[a]

entry	solvent	T	yield[b]	trans:cis[c]	ee (%)[d]
1	THF	rt	91	4:1	71
2	ether	rt	93	5:1	78
3	DME	rt	89	1:1	4
4	toluene	rt	91	4:1	70
5	$CHCl_3$	rt	65	6:1	86
6	DCM	rt	95	10:1	90
7	DMF	rt	83	1:1	4
8[e]	DCM	rt	86	6:1	79
9[f]	DCM	rt	trace		
10	DCM	−20 °C	91	7:1	83
11	DCM	−60 °C	93	5:1	78
12[g]	DCM	rt	88	3:1	57

[a]NHC precursor **4d** (0.03 mmol), Cs_2CO_3 (0.03 mmol), alkylenyloxindole **1a** (0.3 mmol), and ketene **2a** (0.45 mmol) were used. [b]Total yields of the *cis*- and *trans*-isomer. [c]Determined by ^{1}H NMR of the reaction mixture. [d]ee of *trans*-(+)-**3aa**. [e]^{t}BuOK was used as the base. [f]DBU was used as the base. [g]5 mol % of NHC precursor (0.015 mmol) and Cs_2CO_3 (0.015 mmol) were utilized.

TABLE 3. Catalytic Enantioselective Synthesis of 3,4-Dihydropyrano-[2,3-*b*]indol-2-ones via NHC-Catalyzed [4+2] Cycloaddition of 3-Alkylenyloxindoles and Ketenes



entry	1	2 (Ar, R)	3	yield (%)[a]	trans:cis[b]	ee (%)[c]
1	**1a**	**2a** (Ph, Et)	**3aa**	95	10:1	90
2	**1a**	**2b** (Ph, Me)	**3ab**	97	8:1	83
3	**1a**	**2c** (Ph, *n*-Pr)	**3ac**	92	6:1	87
4	**1a**	**2d** (Ph, *n*-Bu)	**3ad**	88	6:1	83
5	**1a**	**2e** (4-MeC_6H_4, Et)	**3ae**	92	6:1	88
6	**1a**	**2f** (4-$MeOC_6H_4$, Et)	**3af**	98	7:1	89
7	**1a**	**2g** (4-ClC_6H_4, Et)	**3ag**	99	9:1	70
8	**1a**	**2h** (4-BrC_6H_4, Et)	**3ah**	97	6:1	69
9	**1a**	**2i** (2-ClC_6H_4, Et)	**3ai**	trace		
10	**1a**	**2j** (2-naphthyl, Et)	**3aj**	trace		
11	**1b**	**2a**	**3ba**	91	3:1	87
12	**1c**	**2a**	**3ca**	92	10:1	83

[a]Total yields of the *cis*- and *trans*-isomer. [b]Determined by ^{1}H NMR of the reaction mixture. [c]Determined by chiral HPLC.

(entries 8 and 9). Other NHCs, such as the tetracyclic NHCs **5a′**,**b′**[21] and bistriazolium NHC **6′**,[22] can also catalyze the reaction efficiently but with low enantioselectivities (entries 10−12).

The optimization of other reaction conditions is summarized in Table 2. Solvent screening revealed that DCM is the solvent of choice, in which good yield (95%) and high diastereoselectivity and enantioselectivity (*trans*:*cis* = 10:1, 90% ee) were achieved (entry 6). It was found that the base of Cs_2CO_3 led to better results than KO^{t}Bu and DBU (entries 8 and 9). Reactions at low temperatures (−20, −60 °C) went well but showed somewhat low diastereo- and enantioselectivities (entries 10, 11). Reducing the loading of the catalyst

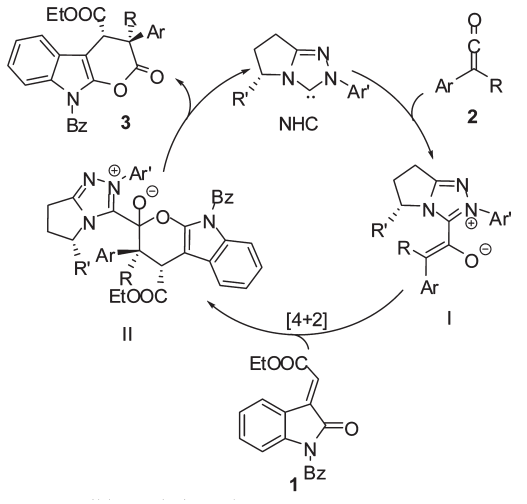


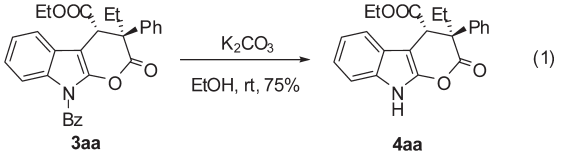
FIGURE 2. Possible catalytic cycle.

to 5 mol % resulted in a descrease in diastereo- and enantioselectivity (entry 12).

With the optimal reaction conditions in hand, the scope of the substrate was then investigated (Table 3). While phenyl(alkyl)ketenes **2a**−**d** with a linear chain (R = Me, Et, *n*-Pr, *n*-Bu) worked well, the yields and selectivities decreased somewhat when the chain was enlongated (entries 1−4). Although the yields are very good for reactions of both aryl(alkyl)-ketenes with electron-donating groups (**2e**,**f**: Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$) and electron-withdrawing groups (**2g**,**h**: Ar = 4-ClC_6H_4, 4-BrC_6H_4), the enantioselectivities decreased somewhat for ketenes **2g**,**h** (entries 5−8). It also should be noted that ketenes with sterically demanding aryl groups (**2i**,**j**: Ar = 2-chlorophenyl, 2-naphthyl) did not work for the reaction (entries 9 and 10).[23]

Other 3-alkylenyloxindoles, such as **1b** and **1c**, with 5-fluoro and 5-methyl substituents, respectively, also worked for the reaction. Although good enantioselectivities were found for both reactions, the diastereoselectivities varied from a ratio of 3:1 to 10:1(entries 11 and 12).

The structure and absolute stereochemistry of dihydropyranoindolone (+)-(3*S*,4*R*)-**3ag** were established by the X-ray analysis of its crystal.[24]



(1)

The benzoyl protective group of the cycloadduct **3aa** could be easily removed to give the corresponding indole-fused dihydropyranone **4aa** in good yield (eq 1).

The possible catalytic cycle is depicted in Figure 2. The addition of NHC to ketenes gives the enolates I, which react with 3-alkylenyloxindoles via [4+2] cycloaddition to give adducts II, followed by fragmentation to furnish the final dihydropyranoindolones **3** and regenerate the NHC.

(21) Kerr, M. S.; Alaniz, J.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725.

(22) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Liu, J.; Yang, S.; You, J.-S. *Adv. Synth. Catal.* **2008**, *350*, 2645.

(23) Monosubstituted ketenes such as phenylketene and chloromethylketenes, generated in situ from the corresponding acyl chlorides, did not work under the current reaction conditions.

(24) See Supporting Information for details.

In conclusion, a high enantioselective synthesis of 3,4-dihydropyrano[2,3-*b*]indol-2-ones was realized by the chiral NHC-catalyzed formal [4+2] cycloaddition of ary(alkyl)-ketenes and 3-alkylenyloxindoes. The ready availability of the catalyst, mild reaction condition, and good selectivities make this direct formal cycloaddition reaction highly potentially useful in the synthesis of the fused indole compounds.

Experimental Section

General Procedure for Synthesis of 3,4-Dihydropyrano[2,3-*b*]indol-2-ones via NHC-Catalyzed Cycloaddition of Ketenes and 3-Alkylenyloxindoles. An oven-dried 50 mL Schlenk tube equipped with a stir bar was charged with the NHC precursor **4d** (22 mg, 0.03 mmol) and Cs_2CO_3 (9.8 mg, 0.03 mmol). The tube was closed with a septum, evacuated, and backfilled with argon. To this mixture was added distilled solvent DCM (2 mL); then the mixture was stirred for 30 min at room temperature. 3-Alkylenyloxindole **1** (0.3 mmol) and ketene **2** (0.45 mmol) were added. The reaction mixture was stirred at room temperature and monitored by TLC until the 3-alkylenyloxindole was fully consumed. The reaction mixture was passed through a pad of silica gel and washed with ethyl acetate. Several drops of the solution were collected and concentrated for the ^{1}H NMR to determine the ratio of the *trans*/*cis*-isomers. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give the corresponding 3,4-dihydropyrano[2,3-*b*]-indol-2-ones as white solids.

3aa: 133.7 mg (95%), R_f = 0.65 (petroleum ether/ethyl acetate, 5:1); mp 169 °C; $[\alpha]^{25}_D$ +242.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.29−7.40 (m, 5H), 7.18−7.28 (m, 4H), 7.11 (d, J = 7.2 Hz, 2H), 4.59 (s, 1H), 4.09−4.24 (m, 2H), 2.20−2.32 (m, 1H), 1.90−2.1 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 167.4, 166.6, 143.2, 135.5, 133.8, 133.0, 132.3, 129.4, 128.8, 128.2, 128.1, 126.9, 125.0, 124.2, 124.0 117.3, 114.9, 93.5, 62.0, 52.6, 41.9, 29.6, 14.0, 7.5; IR (KBr) ν 1786, 1734, 1698 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{25}NO_5$ $[M]^+$ 467.1733, found 467.1738. HPLC analysis: 90% ee (*trans*) [Daicel CHIRALPAK AD-H column; 20 °C; 1.0 mL/min; solvent system: *i*-PrOH/hexanes, 10:90; retention times: 13.9 min (minor), 16.0 min (major)].

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Supporting Information Available: Experimental procedures, compound characterizations (PDF), and crystal structure data of indolodihydropyranone **3ag** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.