Carbocycles

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Catalytic [4+2] Cyclization of α,β-Unsaturated Acyl Chlorides with 3-Alkylenyloxindoles: Highly Diastereo- and Enantioselective Synthesis of Spirocarbocyclic Oxindoles**

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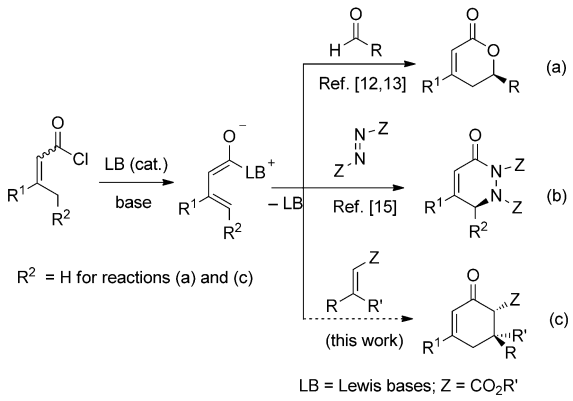
The spirooxindole is a privileged structure moiety found in many biologically active natural products and pharmaceutically active compounds.[1] Thus, many elegant approaches have been developed for its construction.[2] Typical intramolecular approaches are the oxidative rearrangement of tetrahydro-β-carbolines,[3] and the palladium-catalyzed Heck reaction.[4] The intermolecular cyclization, which forms two or more C–C bonds in one pot, is very interesting for the construction of cyclic compounds, because it is a step-economic approach and the starting materials are relatively readily available.[5] Trost and co-workers reported a palladium-catalyzed [3+2] cyclization of 3-alkenyloxindole with trimethylenemethane, leading to the spirocyclic oxindolic cyclopentanes in good yields with high enantioselectivities.[6] A facile synthesis of spirooxindole, developed by Carreira and co-workers, involves the formal [3+2] cyclization of spirocyclopropane with aldimines.[7] Recently, several efficient routes to spirocyclic oxindole by the chiral amine-catalyzed cascade process were reported, including the [4+2] cyclization through double Michael addition,[8] the [4+2] or [3+2] cyclization through Michael–aldol process,[9] and the three-component [2+2+2] cyclization.[10] Moreover, Lu and co-workers reported an interesting phosphine-catalyzed highly enantioselective [3+2] cyclization of 3-alkenyloxindoles with Morita–Baylis–Hillman adducts.[11]

Recently, the cyclization reaction of α,β-unsaturated acyl chlorides catalyzed by chiral Lewis bases emerges as a powerful tool for the construction of cyclic compounds (Scheme 1). In 2007, Peters and co-workers reported the pioneering cinchona alkaloids catalyzed [4+2] cyclization of unsaturated acyl halides with aldehydes (Scheme 1, reaction a).[12] Our group reported the N-heterocyclic carbene catalyzed cyclization of α,β-unsaturated acyl chloride and activated ketones or nitroso compounds.[13,14] Lately, the highly enantioselective [4+2] cyclization of α,β-unsaturated acyl chlorides with azodicarboxylates was realized in our group (Scheme 1, reaction b).[15] Compared to the well-established catalytic cyclizations of α,β-unsaturated acyl chlorides with unsaturated C–O or N–N bonds, the corresponding reaction with unsaturated C–C bonds remains a challenge (Scheme 1, reaction c). Herein, we report a catalytic [4+2] cyclization that includes only carbon atoms of α,β-unsaturated acyl chlorides with electron-deficient alkenes derived from oxindole for the construction of spirocarbocyclic oxindoles.



Scheme 1. Lewis base catalyzed cyclization of α,β-unsaturated acyl chlorides.

Initially, the N-heterocyclic carbene (NHC)-catalyzed [4+2] cyclization of α,β-unsaturated acyl chloride **1a** and 3-alkylenyloxindole **2a** was investigated. We are happy to find that NHC **4a** could catalyze the reaction to give the desired cycloadduct **3a** in good yield with high diastereoselectivity (Table 1, entry 1). However, the reaction catalyzed by chiral NHC **5a** gave cycloadduct **3a** in nearly racemate form (Table 1, entry 2). Several chiral NHCs, derived from L-pyroglutamic acid and aminoindanol, were tested but without notable enantioselectivity observed.

The cinchona alkaloids were then chosen as Lewis base catalyst for the reaction. We were happy to find that cycloadduct **3a** was obtained in 90% yield with 15:1 d.r. for the reaction catalyzed by *O*-TMS quinidine **6a** (TMS-QD; Table 1, entry 3). Other quinidine derivatives **6b** (Bn-QD) and **6c** (*t*Bu-QD) also worked well but led to low enantioselectivity (Table 1, entries 4 and 5). Solvent screening revealed that THF is the best choice compared to ethyl ether, CH_2Cl_2, DMF, and toluene (Table 1, entries 3, 6–9). When the reaction temperature was lowered from −10 °C to −78 °C, better diastereoselectivity and enantioselectivity were obtained and the yield was not affected (Table 1,

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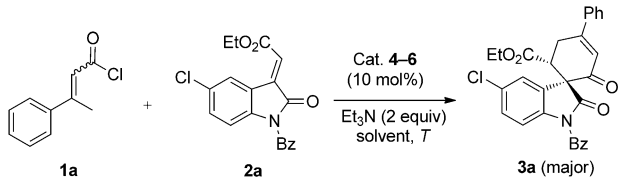
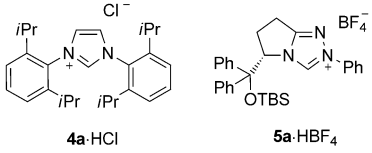
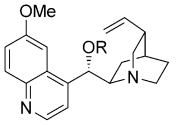
Table 1: Optimization of reaction conditions.



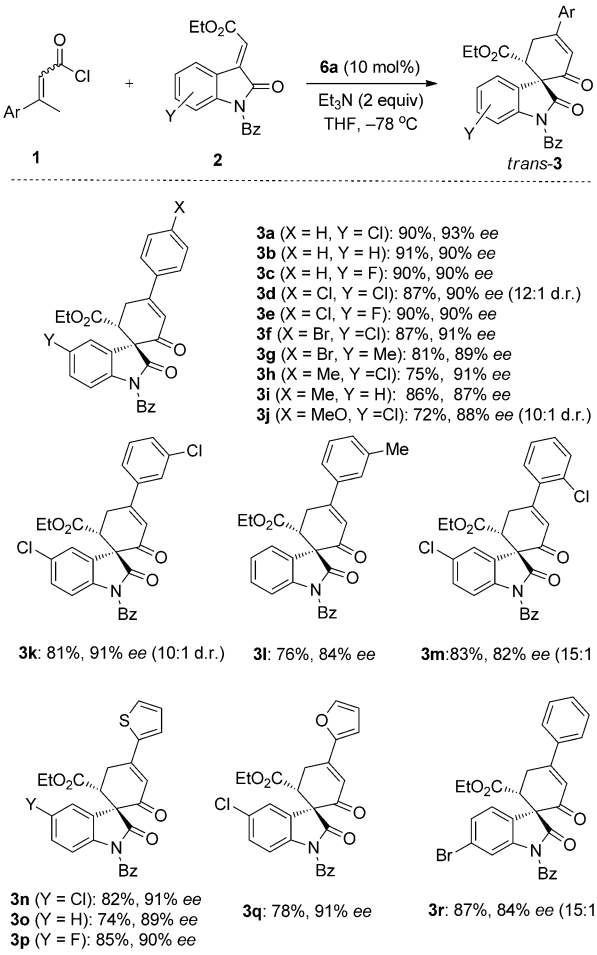
Entry	Cat.[a,b]	Solvent	*T* [°C]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**4a**	THF	−10	80	15:1	/
2	**5a**	THF	−10	87	18:1	2
3	**6a**	THF	−10	90	15:1	83
4	**6b**	THF	−10	89	8:1	26
5	**6c**	THF	−10	86	15:1	53
6	**6a**	ethyl ether	−10	32	2:1	56
7	**6a**	CH_2Cl_2	−10	78	5:1	45
8	**6a**	DMF	−10	17	3:1	65
9	**6a**	toluene	−10	35	2:1	32
10	**6a**	THF	−78	90	>20:1	89
11[f]	**6a**	THF	−78	90	>20:1	93

[a] NHCs **4a**–**5a** were freshly generated from the corresponding azolium salt in the presence of Cs_2CO_3 at room temperature for 30 min, and used immediately. [b] The hydrochloride salt of quinidine derivative was used for easy manipulation. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy (300 MHz). [e] Determined by HPLC using a chiral stationary phase. TMS = trimethylsilyl. [f] Acyl chloride was added over four hours by using a syringe pump.





6a R = TMS (TMS-QD)
6b R = Bn (Bn-QD)
6c R = *t*Bu (*t*Bu-QD)



Scheme 2. Enantioselective [4+2] annulation of α,β-unsaturated acyl chlorides and 3-alkylenyloxindoles. The yields of isolated products **3** and the *ee* values determined by HPLC are given. Unless otherwise noted d.r. > 20:1.

entry 10). The enantioselectivity was further improved to 93% *ee* when the acyl chloride was added slowly (Table 1, entry 11).

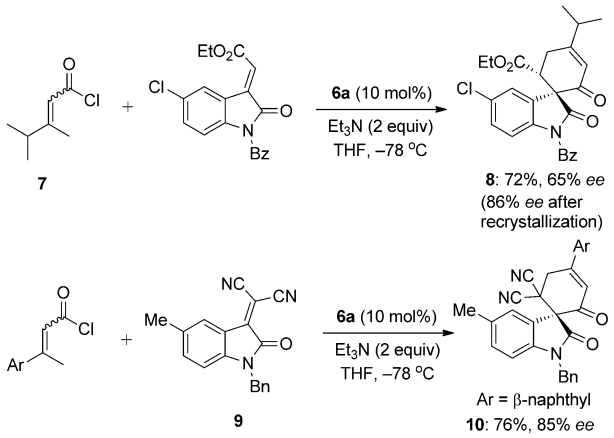
With the optimized reaction conditions in hand, the scope of α,β-unsaturated acyl chlorides and 3-alkylenyloxindoles was briefly investigated (Scheme 2). It was found that both β-aryl-α,β-unsaturated acyl chlorides with electron-withdrawing groups (Ar = 4-Cl, 4-BrC_6H_4) and with electron-donating groups (Ar = 4-Me, 4-MeOC_6H_4) all worked well to give the desired cycloadducts (**3a**–**3j**) in good yields with high diastereoselectivities and enantioselectivities. 3-Substituted (Ar = 3-Cl, 3-MeC_6H_4,) and 2-substituted (Ar = 2-ClC_6H_4) phenyl groups were also tolerable for the reaction (**3k**–**3m**) albeit with some decreased enantioselectivities for cycloadducts **3l** and **3m**. Furthermore, α,β-unsaturated acyl chlorides with β-heteroaryl groups, such as 2-furyl and 2-thienyl, also worked very well (**3n**–**3q**) to give the desired cycloadduct in good yields with high diastereo- and enantioselectivity.

Several 3-alkylenyloxindole derivatives have also been tested for the reaction. Beside 5-chlorooxindole derivative **2a**, other 5-substituted derivatives, such as 5-fluoro- and 5-methyl-3-alkylenyloxindoles, also worked well to give the desired cycloadducts (**3c**, **3e**, **3g**, and **3p**) in high yields with high diastereo- and enantioselectivities. Reaction of the 6-bromooxindole derivative gave the corresponding cycloadduct **3r** in good yield with 15:1 d.r. and 84% *ee*.

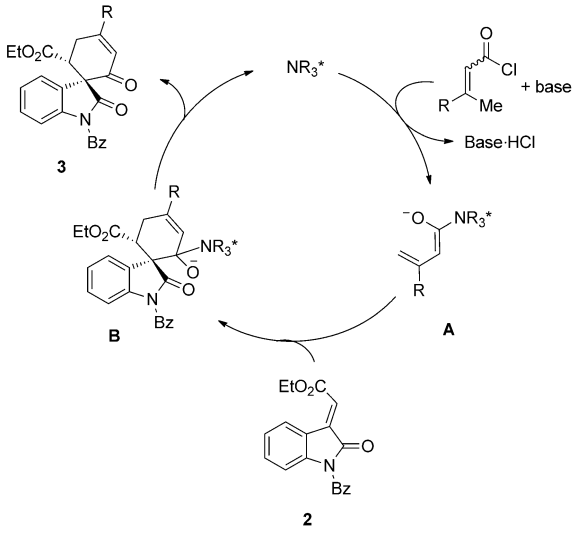
The scope of the reaction was further expanded for more varied substrates (Scheme 3). It was found that reaction of β-isopropyl-α,β-unsaturated acyl chloride **7** went smoothly to give the corresponding cycloadduct **8** in 72% yield with excellent diastereoselectivity and 65% *ee*. The enantiopurity of **8** could be improved to 86% *ee* after one recrystallization. Furthermore, doubly activated alkenes **9** derived from oxindole and malononitrile also worked well to afford the corresponding cycloadduct **10** in 76% yield with 85% *ee*.

The structures of spirocarbocyclic oxindole (+)-**3a** and *rac*-**3i** were unambiguous established by the X-ray analysis of their crystals (Figures S1 and S2 in the Supporting Information).[16]

The plausible catalytic cycle of this cinchona alkaloid catalyzed all-carbon-[4+2] annulations is depicted in Scheme 4. Dienolate **A** is generated from α,β-unsaturated acyl chloride **1** and tertiary amine catalyst in the presence of base. The dienolate **A** reacts with 3-alkylenyloxindole **2** in a Diels–Alder-type reaction or a stepwise vinylogous aldol reaction with subsequent intramolecular cyclization, to give



Scheme 3. Reaction with β-isopropyl-α,β-unsaturated acyl chloride **7** or doubly activated alkene **9**.



Scheme 4. Plausible catalytic cycle.

zwitterionic intermediate **B**. The observed exclusive or very high *trans* selectivity suggests that the Diels–Alder reaction pathway is favored over the stepwise pathway.[17] The collapse of zwitterion **B** furnishes final cycloadduct **3** and regenerates the catalyst.

In conclusion, the cinchona alkaloids catalyzed all-carbon-[4+2] cyclization of α,β-unsaturated acyl chlorides with electron-deficient alkenes derived from oxindole was developed to give the corresponding spirocarbocyclic oxindoles in good yields with high diastereo- and enantioselectivities. Studies of more Lewis bases catalyzed cyclization reactions of α,β-unsaturated acyl chlorides are under way.

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[16] The crystal was prepared from the solution in petroleum ether/ethyl acetate, with a trace of chloroform. CCDC 900492 ((+)-**3a**), 892111 (*rac*-**3i**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[17] The epimerization of *trans*-**3** to *cis*-**3** under the reaction conditions was observed with elongated reaction time, which accounts for the presence of some *cis*-product in some cases.

