Catalytic Generation of Donor-Acceptor Cyclopropanes under *N*-Heterocyclic Carbene Activation and their Stereoselective Reaction with Alkylideneoxindoles

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Catalytic Generation of Donor-Acceptor Cyclopropanes under *N*-Heterocyclic Carbene Activation and their Stereoselective Reaction with Alkylideneoxindoles

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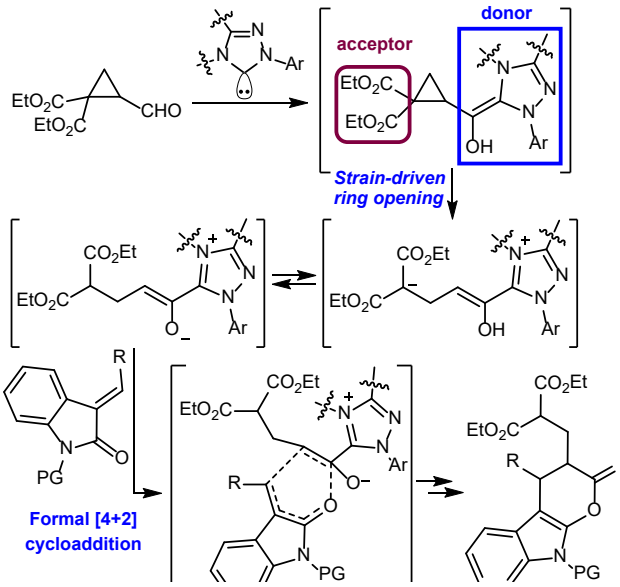
Abstract. Formylcyclopropanes undergo activation in the presence of an *N*-heterocyclic carbene catalyst generating a donor-acceptor cyclopropane intermediate with the ability to undergo ring-opening followed by formal [4+2] cycloaddition with alkylideneoxindoles. This enables the direct enantio- and diastereoselective synthesis of tetrahydropyrano[2,3-*b*]indoles through the use of a chiral NHC catalyst.

Keywords: Asymmetric Catalysis; Cycloaddition; Cyclopropanes; N-Heterocyclic Carbenes

The use of cyclopropanes as reagents in synthesis has experienced a renaissance in the last few years.[1] The strain energy associated to the cyclopropane ring and the tendency to release this strain through ring-opening has been used as useful platform to find unusual reactivity profiles. In particular, cyclopropanes which are simultaneously substituted with an electron-donating and an electron-withdrawing group are particularly attractive because the synergistic electronic nature of these substituents strongly favours the ring-opening process, generating an intermediate with potential to undergo a wide range of subsequent reactions.[2] In this sense, most reports involve the use of Lewis acids as promoters of the ring-opening event, which has also been applied to enantioselective versions through the incorporation of a chiral ligand. In contrast to the important number of reports that make use of this approach, the alternative capacity of organocatalysts to activate these strained substrates has only been very recently documented. In particular, there are some precedents showing the application of iminium,[3] enamine[4] and H-bonding activation[5] to initiate the ring-opening event on carefully designed cyclopropane substrates. Several reports also illustrate the ability of *N*-heterocyclic carbenes to catalyze reactions with formylcyclopropanes but these are either non-enantioselective versions[6] or, alternatively, are reactions of rather limited scope.[7]

With all these precedents in mind, we directed our attention to the capacity of *N*-heterocyclic carbenes[8] to catalytically generate a donor-acceptor cyclopropane upon interaction with a formylcyclopropane incorporating two electron-withdrawing groups at the three-membered ring (Scheme 1). The condensation between the carbene with the formyl group would generate the corresponding Breslow intermediate in which the enaminol moiety would operate as the electron-donating substituent, therefore facilitating the subsequent ring-opening event. The resulting intermediate would have the capacity to undergo formal [4+2] cycloaddition with a suitable substrate such as an alkylideneoxindole.[9] The overall process would result in a useful catalytic and enantioselective approach to the tetrahydropyrano[2,3-*b*]indole substructure, which is a relevant scaffold present in compounds with interesting biological activities.[10]

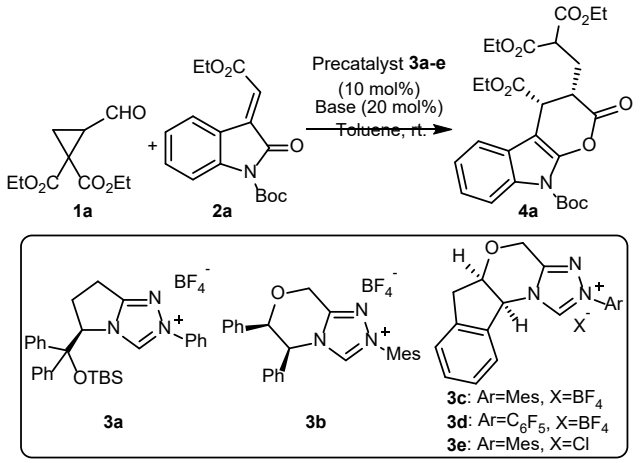


Scheme 1. Catalytic generation of D-A cyclopropanes and their reactivity towards alkylideneoxindoles.

We started our studies by surveying a variety of chiral trazolium salts **3a-e** as the *N*-heterocyclic

carbene precursor, using the reaction between formylcyclopropane 1a and alkylideneoxindole **2a** as model substrates (Table 1). We initially surveyed a set of triazolium catalysts with different chiral backbone structures (precatalysts **3a-c**, entries 1-3), observing that aminoindol-based precatalyst **3c** provided excellent results in terms of stereocontrol, and furnishing cycloadduct **4a** in a promising 60% yield (entry 3).

Table 1. Optimization of the reaction conditions.[a)]

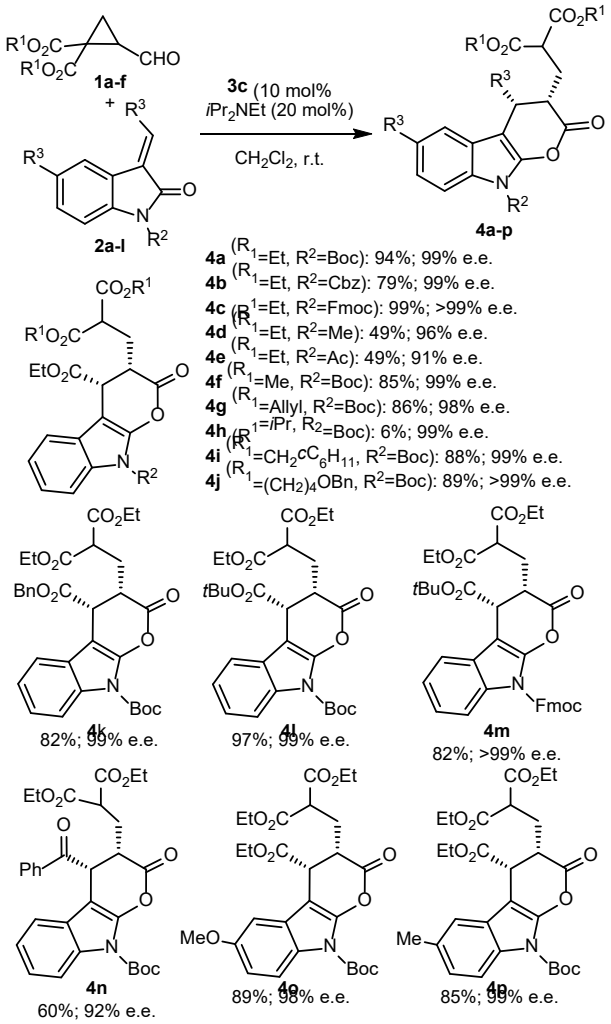


Entry	**3**	Base	Solvent	Yield (%)	d.r.[b)]	e.e. (%)[c)]
1	**3a**	Et_3N	Toluene	<5	n.d.[d)]	n.d.[d)]
2	**3b**	Et_3N	Toluene	25	>20:1	46
3	**3c**	Et_3N	Toluene	60	>20:1	99
4	**3d**	Et_3N	Toluene	<5	n.d.[d)]	n.d.[d)]
5	**3e**	Et_3N	Toluene	52	>20:1	99
6	**3c**	K_2CO_3	Toluene	22	>20:1	92
7	**3c**	DBU	Toluene	57	>20:1	98
8	**3c**	*i*Pr_2NEt	Toluene	66	>20:1	99
9	**3c**	*i*Pr_2NEt	THF	18	n.d.[d)]	n.d.[d)]
10	**3c**	*i*Pr_2NEt	*n*Hexane	<5	n.d.[d)]	n.d.[d)]
11	**3c**	*i*Pr_2NEt	CH_2Cl_2	94	>20:1	99

[a)] Reaction carried out using 0.30 mmol of **1a**, 0.20 mmol of **2a**, 10 mol% of precatalyst **3** and 20 mol% of base in 2 mL of solvent at rt for 3 h. [b)] Determined by ^{1}H NMR analysis of crude reaction mixture. [c)] Determined by HPLC in a chiral stationary phase (see SI for details). [d)] n.d.: not determined.

Changing the aryl substituent from mesityl to pentafluorophenyl substituent (**3d**, entry 4) resulted in the complete deactivation of the catalyst towards the reaction, in line with previous reports that indicate that the mesityl substituent accelerates those reactions involving the activation of α-functionalized aldehydes under NHC catalysis.[11] The counteranion of the triazolium salt did not show to have a relevant impact on the performance of the reaction, as it can be seen with the experiment using precatalyst **3e** (entry 5). We next surveyed different bases for the generation of the carbene active species (entries 6-8), observing a slight increase in the yield of the reaction when *i*Pr_2EtN was used (entry 8) without decreasing the high stereocontrol obtained before. Finally, other solvents were also examined (entries 9-11), observing that the use of a highly polar solvent like THF resulted in poor yield of cycloadduct **4a** (entry 9), while a nonpolar solvent like hexane led to no reaction after prolonged stirring of the reaction mixture (entry 10). Remarkably, slightly increasing the polarity from toluene to CH_2Cl_2 led to a significant improvement of the yield of the reaction, furnishing **3a** as a single diastereoisomer of very high enantiopurity (entry 11).

With an optimized experimental protocol for the reaction in hand, we next proceeded to explore the scope of the reaction with respect to the formylcyclopropane and the alkylideneoxindole reagents (Scheme 2).



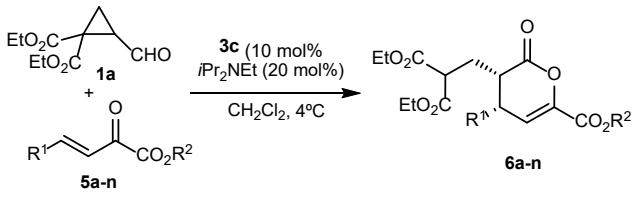
Scheme 2. Scope of the reaction.

As it can be seen in this scheme, the reaction performed excellently regardless the nature of the protecting group at the indole moiety, although *N*-alkyl substituted alkylideneoxindoles provided inferior yields than those with an *N*-carbamate protecting group. In the same line, the reaction also tolerated well the incorporation of different

substituents at the two ester groups on the starting cyclopropane **1** (adducts **4a-4j**), although very bulky groups like *i*Pr turned into very poor conversion (adduct **4i**). Changing the nature of the β-substituent at the alkylideneoxindole scaffold was also feasible, being the reaction also very effective with different ester groups (compounds **4k-4m**) and also with a benzoyl substituent (compound **4n**). Finally, different substituents could also be successfully incorporated at the aryl moiety of the alkylideneoxindole reagent (compounds **4o** and **4p**). In all cases adducts **4a-4p** were isolated as single diastereoisomers with enantioselectivities over 90% e.e. The absolute configuration of compound **4k** was established by X-ray analysis of a monocrystalline sample[12] and this was extended to all other adducts **4a-4p** based on mechanistic analogy.

We also decided to explore the possibility of carrying out the reaction using β,γ-unsaturated α-ketoesters as highly reactive Michael acceptors in this formal [4+2] cycloaddition process (Table 2). In fact, the reaction performed excellently with a variety of substrates **5a-5n** using the same catalyst **3a** and under closely related conditions, only requiring lowering down the temperature of the reaction.

Table 2. Reaction using β,γ-unsaturated α-ketoesters.[a)]



Entry	6	R^1	R^2	Yield (%)	d.r.[b)]	e.e. (%)[c)]
1	**6a**	Ph	Me	73	>20:1	97
2	**6b**	Ph	Et	77	>20:1	>99
3	**6c**	4-FC_6H_4	Me	72	>20:1	>99
4	**6d**	4-$MeOC_6H_4$	Me	81	>20:1	>99
5	**6e**	4-MeC_6H_4	Me	85	>20:1	99
6	**6f**	3-MeC_6H_4	Me	82	>20:1	99
7	**6g**	2-MeC_6H_4	Me	66	>20:1	>99
8	**6h**	3,4-OCH_2O-C_6H_3	Me	78	>20:1	>99
9	**6i**	2-furyl	Me	46	2:1	>99
10	**6j**	2-thienyl	Me	68	2:1	>99
11	**6k**	Me	Et	83	>20:1	>99
12	**6l**	*i*Pr	Et	85	>20:1	>99
13	**6m**	CH_2OBn	Et	58	>20:1	>99
14	**6n**	CH_2CH_2Ph	Et	72	>20:1	97
15[d)]	**6e**	4-MeC_6H_4	Me	82	>20:1	99

[a)] Reaction carried out using 0.20 mmol of **1a**, 0.20 mmol of **5**, 10 mol% of precatalyst **3** and 20 mol% of base in 2 mL of solvent at 4°C for 24-36 h. [b)] Determined by ^{1}H NMR analysis of crude reaction mixture. [c)] Determined by HPLC in a chiral stationary phase (see SI for details). [d)] 5 mol% of catalyst and 10 mol% of base were used.

As it can be seen in table 2, cycloadducts **6a-6e** were obtained in high yields and stereocontrol regardless the nature of the ester substituent at the β,γ-unsaturated-α-ketoester reagent **5** (entry 1 *vs* 2) and the reaction also performed excellently for substrates with a wide range of substitution patterns at the γ-position, including aryl groups with either electron-withdrawing or electron-donating groups located at different positions of the aryl moiety (entries 3-8). Substrates with γ-heteroaryl substituents also provided the corresponding adducts with good yield and enantioselectivity, although as 2:1 mixtures of diastereoisomers (entries 9 and 10). Moreover, the very challenging γ-alkyl-substituted β,γ-unsaturated-α-ketoesters also performed very well in the reaction, furnishing the corresponding cycloadducts in high yields, diastereo- and enantioselectivities (entries 11-14). Remarkably, we could also demonstrate that the reaction can be carried out using a lower catalyst loading (entry 15), just requiring to stir the mixture for a longer time (36 *vs* 60 h). The absolute stereostructure of these 3,4-dihydro-2*H*-pyran-2-one adducts **6** was also established by X-ray analysis of monocrystals grown for compound **6b**,[13] extending the obtained absolute configuration to the other derivatives **6a-n** by assuming the same mechanistic pathway for all cases.

In conclusion, formylcyclopropanes with two electron-withdrawing alkoxycarbonyl substituents are able to undergo condensation with an *N*-heterocyclic carbene catalyst, generating the corresponding Breslow intermediate that subsequently undergoes strain-driven ring-opening followed by formal [4+2] cycloaddition with an activated alkene such as an alkylideneoxindole or a β,γ-unsaturated α-ketoester. In the presence of precatalyst **3c** and under optimized conditions, the reaction proceeds with excellent yield, diastereo- and enantioselectivity for a variety of substrates tested.

Experimental Section

General Methods and Materilas

NMR: Monodimensional nuclear magnetic resonance proton, carbon and fluoro spectra (^{1}H NMR, ^{13}C NMR and ^{19}F) were acquired at 25ºC on a Bruker AC-300 spectrometer (300 MHz for ^{1}H, 75.5 MHz for ^{13}C and 282 MHz for ^{19}F). IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100 in the interval between 4000 and 400 cm-1 with a 4 cm^{-1} resolution. MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer under electronic impact (EI). HRMS: High-resolution mass spectra (HRMS) on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI+ or ESI-). M.p.: Melting points were measured in a Büchi B-540 apparatus in open capillary tubes and are uncorrected. HPLC: High performance liquid chromatography on a chiral stationary phase was performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak AD-H, IA, IC, OD-H columns (0.46 cm x 25 cm) were used in specific conditions indicated for each case. X-ray data collections were performed in an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250μm FWHM beam size). The sample was kept at 120 K with a Oxford

Cryosystems Cryostream 700 cooler. Miscellaneous: Analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.

General Procedures for the Preparation of [2,3-*b*]indole adducts 4a-p

Into as oven-dryed, screw-capped vial equipped with a magnetic stir bar, the triazolium salt **3c** (0.02 mmol, 0.1 equiv) was weighed. The vial was capped with a septum cap and purged with argon for 5 min. Then, to the vial under positive argon pressure, were successively added CH2Cl2 (1 mL), *N*,*N*-diisopropylethylamine (0.04 mmol, 0.2 equiv), the corresponding formilcyclopropane dicarboxylate **1a-f** (0.30 mmol, 1.5 equiv) in solution of CH2Cl2 (1 mL) via syringe and the corresponding 3-methylene-2-oxindol **2a-k** (0.20 mmol, 1.0 equiv) was added as a solid removing the septum cap and stirred at 23 ºC for 3 h. The crude reaction mixture was concentrated and directly charged onto silica gel and subjected to flash chromatography (hexane/EtOAc gradient from 19:1 to 9:1), affording the corresponding adducts **4a-p**. Racemic samples were obtained following the same protocol but with 2-(pentafluorophenyl)-6,7-dihydro-5H-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (0.1 mmol, 0.1 equiv) as catalyst.

General Procedures for the Preparation of Lactones 6a-6n

An ordinary vial was charged with pre-catalyst **3c** (0.02 mmol, 10 mol%) equipped with a magnetic stirring bar and put under an argon atmosphere. Dichloromethane (1 mL) was added followed by *N*,*N*-diisopropylethylamine (7 µL, 20 mol%) and the mixture was stirred for 10 min at room temperature. The vial was then placed at 5 ºC and stirred for further 10 min prior to the addition of aldehyde **1** (0.30 mmol) in dichloromethane (1 mL) and ketoester **5** (0.20 mmol). The stirring was maintained at this temperature until the reaction was complete. Solvents were evaporated and the crude was charged onto silica gel and subjected to FC. Racemic standards for HPLC separation conditions were prepared using 2-(pentafluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (0.02 mmol, 10 mol%) as pre-catalyst and running the reaction at room temperature.

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