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N-Heterocyclic Carbene and Chiral Brønsted Acid Cooperative Catalysis for a Highly Enantioselective [4+2] Annulation

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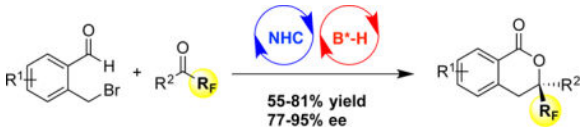
Abstract

A chiral NHC/Brønsted acid cooperative catalysis system has been developed for asymmetric annulation of functionalized benzaldehydes and activated ketones through dearomative generation of dienolate.

Graphical abstract



Keywords

NHC; Brønsted acid; cooperative; annulation

N-Heterocyclic Carbene (NHC) catalysis has been the focus of asymmetric organocatalysis for decades, featuring in umpolung transformations of aldehydes and effective activation of other carbonyls.[1] One of the significant advantages of carbene catalysis is its incredible compatibility[2] with other organocatalysts[3–7] as well as metal catalysts.[8–9] We have previously disclosed a productive carbene/Brønsted acid cooperative catalysis for highly enantioselective synthesis of *trans*-γ-lactams from α, β-unsaturated aldehydes and unactivated imines,[5] a concept that has proven to be broad.[6]

Recently, a dienolate intermediate generated through NHC catalysis, either from linear α, β-unsaturated carbonyls with installed leaving groups (Scheme 1a, path I) or from aldehydes under oxidative conditions (Scheme 1a, path II), has been comprehensively studied by Ye,[10] Chi[11] and others.[12] In 2013, Chi[13] and coworkers reported a NHC-catalyzed oxidative formal [4+2] cycloaddition of heteroaryl aldehydes and activated ketones. The benzaldehyde analogue was nonproductive in Chi's reaction. We hypothesized that a leaving group at the

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Dedicated to Professor Dieter Enders, a pioneer in NHC catalysis, on the occasion of his 70th birthday.

Supporting Information

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Primary Data

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benzylic position would facilitate this process in a redox fashion (Scheme 1b).[14] Herein, we report a highly enantioselective [4+2] annulation of 2-(bromomethyl)benzaldehydes and fluorinated ketones by the action of NHC/phosphoric acid cooperative catalysis.

Starting with 2-(bromomethyl)benzaldehyde **1a** and trifluoroacetophenone **2a** as the substrates, use of achiral triazolium salt **4** gave desired product **3a** in 57% yield (Table 1, entry 1). We then evaluated chiral carbene precursors (entries 2–4) and found that our aminoindanol-derived triazolium salt **5a** with *N*-pentafluorophenyl group provided the best reactivity (entry 2). Further screening of solvents and bases disclosed that reaction with **5a** and KOAc in cyclohexane was more efficient (61% yield and 76% ee, entry 6). Reaction of 2- (chloromethyl)benzaldehyde **1b** and **2a** led to the same product, but yield and enantioselectivity were both lower (entry 7).

Various additives were then investigated under otherwise identical conditions (Table 2). Molecular sieves with different pore diameters generally lower the yields albeit with slightly higher ee (entries 1–3). Lewis acids compatible with chiral NHCs, such as LiCl and $Sc(OTf)_3$, did not improve the reaction (entries 4–5). Speculating that the slightly improved selectivities observed with acetate as base were due to a potential role of the conjugate acid in the stereoselectivity determining event, we investigated the impact of BINOL-derived chiral phosphoric acid[15] as co-catalyst. We were pleased to find that application of **6a** (20 mol%) delivered 82% ee (entry 6). Steric and electronic variation of 3,3′-aryl substituents of chiral phosphoric acid continued to improve the enantioselectivity (entries 6–9) with **6d**[16] providing an optimized 95% ee (entry 9). Lower catalyst loading of **6d** increased efficiency without erosion of enantioselectivity (entry 10). A combination of *ent*-**5a** with **6d** was found to be less effective, indicating a match/mismatch situation between these two chiral catalysts (entry 11).

With optimal conditions in hand, we firstly explored the ketone scope (Scheme 2, part I). Electron-withdrawing substituents on the aryl ring of trifluoroacetophenones generally decrease the enantioselectivities. For example, reactions of para-fluoro, para-chloro and meta-fluoro analogs with **1a** afford **5b**, **5c** and **5d** in moderate yields and good selectivities. Electron rich trifluoroacetophenones and alkyl trifluoromethyl ketones fail to give any products presumably due to their lower reactivity. Annulations with ketones bearing longer-chain perfluoroalkyl units provide lactones **3e** and **3f** in good yields and enantioselectivities. Ethyl phenylgloxylate, on the other hand, does not participate in this reaction.

We next evaluated bromomethyl aryl aldehyde scope (Scheme 2, part II). Reaction of para-chlorosubstituted system with **2a** provides **3j** in 57% yield, with 90% ee. A phenyl substituent surprisingly had a huge impact on the reactivity. For example, 4-phenylbenzaldehyde delivers product in 66% yield and 77% ee (**3j**) while a 5-phenyl group gives much higher yield and enantioselectivity (**3m**). The use of para-fluorinated analog of **2a** would offset the negative effect brought by 4-phenyl substituent on benzaldehyde, delivering 71% yield and 93% ee (**3l**).

We propose a catalytic cycle as shown in Scheme 3. There is an equilibrium between triazolium salt **5a** and free carbene **5a′** in the presence of acetate.[17] Activation of **1a** by **5a′**

generates a possible zwitterionic intermediate **I**, which undergoes proton transfer to form the Breslow intermediate **II**. Extrusion of the bromide within **II** gives dienolate intermediate **III**, which reacts with the carbonyl via a transition state analogous to **IV**. Formation of an ion pair between triazolium and chiral phosphate counterion would increase its solubility in cyclohexane, implying that the phosphoric acid catalyst may be acting as a chiral counterion although other mechanisms cannot be discounted. As mentioned above, a matched situation between the NHC and phosphoric acid backbone chirality is required for excellent stereocontrol. After C-C bond-forming, a new C-O bond forms through intermediate **V** and releases final product **3a**, and free carbene **5a′** for the new catalytic circle.[18]

In conclusion, we have developed NHC/chiral phosphoric acid cooperative catalysis, enabling a highly enantioselective [4+2] annulation reaction of 2-(bromomethyl)benzaldehydes and fluorinated ketones. The phosphoric acid catalyst may be acting as a chiral Brønsted acid, a chiral counterion or phase transfer agent for the NHC catalyst. Cooperative activation between the NHC catalyst and phosphoric acid would provide new opportunities in asymmetric NHC catalysis and extension of the concept to other annulation modes may be possible.[19]

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker spectrometer (500 MHz, 125 MHz and 471 MHz for ^{1}H, ^{13}C and ^{19}F NMR, respectively) at ambient temperature. High resolution mass spectra (HRMS) were obtained from Columbia University Mass Spectrometry Facility on a JOEL JMSHX110HF mass spectrometer using FAB+ ionization model. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FI-IR spectrometer. HPLC spectra were obtained on an Agilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter.

(*S*)-3-phenyl-3-(trifluoromethyl)isochroman-1-one (3a): Typical Procedure

To an oven-dried 5 mL vial with a magnetic stir bar, aldehyde **1a** (0.10 mmol), ketone **2a** (0.20 mmol), triazolium salt **5a** (9.3 mg, 0.020 mmol), chiral phosphoric acid **6d** (6.8 mg, 0.010 mmol), KOAc (19.6 mg, 0.40 mmol) were added before being transferred to an argon-filled glovebox. 1.0 mL of dry cyclohexane was added. The vial was tightly capped and removed from the glovebox. The reaction was vigorously stirred at room temperature. After 12h, the mixture was concentrated and the residue was subjected to flash silica gel chromatography (hexane: ether = 20:1) to yield lactone **3a** (19.9 mg, 68% yield, 95% ee).

$[\alpha]^{20}_{D}$ = +87.8° (c = 0.014 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 – 7.42 (m, 3H), 7.35 – 7.25 (m, 5H), 3.83 (d, *J* = 16.3 Hz, 1H), 3.69 (d, *J* = 16.3 Hz, 1H). Data matches literature report.[14]

(*S*)-3-(4-fluorophenyl)-3-(trifluoromethyl)isochroman-1-one (3b)

21.4 mg, 69% yield, 91% ee;

$[\alpha]^{20}_{D}$ = +90.9° (c = 0.017 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.35 – 7.25 (m, 2H), 7.06 – 6.93 (m, 2H), 3.84 (d, *J* = 16.3 Hz, 1H), 3.64 (d, *J* = 16.4 Hz, 1H). Data matches literature report.[14]

(*S*)-3-(4-chlorophenyl)-3-(trifluoromethyl)isochroman-1-one (3c)

18.1 mg, 55% yield; 83% ee;

$[\alpha]^{20}_D$ = +75.6° (c = 0.016 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 5.8, 2.9 Hz, 1H), 7.22–7.11 (m, 5H), 6.75–6.72 (m, 3H), 5.07 (s, 1H), 3.80 (dt, *J* = 11.2, 4.9 Hz, 1H), 3.34 (ddd, *J* = 11.1, 10.0, 4.1 Hz, 1H), 3.08 (ddd, *J* = 15.5, 10.1, 5.2 Hz, 1H), 2.91 (dt, *J* = 15.6, 4.3 Hz, 1H), 2.53–2.31 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H). Data matches literature report.[14]

(*S*)-3-(3-fluorophenyl)-3-(trifluoromethyl)isochroman-1-one (3d)

21.1 mg, 68% yield; 87% ee;

$[\alpha]^{20}_D$ = +72.0° (c = 0.014 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.52 (td, *J* = 7.6, 1.3 Hz, 1H), 7.35 – 7.22 (m, 5H), 7.01 (m, 1H), 3.84 (d, *J* = 16.3 Hz, 1H), 3.63 (d, *J* = 16.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7 (d, *J* = 246 Hz), 161.9, 136.1 (d, *J* = 7.1 Hz), 134.9, 134.8, 130.5, 130.4 (d, *J* = 8.1 Hz), 128.3, 127.9, 124.2, 123.0 (q, *J* = 282 Hz), 122.8 (d, *J* = 2.6 Hz), 116.7 (d, *J* = 20.9 Hz), 114.6 (d, *J* = 23.8 Hz) 82.7 (q, *J* = 30.7 Hz), 31.1 (d, *J* = 1.5 Hz);

^{19}F NMR (471 HZ, $CDCl_3$) δ −78.6 (s), −110.3 (m);

IR (neat) 1742, 1594, 1445, 1280, 1185, 1115, 1073, 749, 729, 708 cm^{-1};

HRMS (ESI^+) calcd for $C_{16}H_{11}O_2F_4$ as $[M+H]^+$, 311.0695. Found 311.0696.

(*S*)-3-(perfluoroethyl)-3-phenylisochroman-1-one (3e)

21.6 mg, 63% yield; 87% ee;

$[\alpha]^{20}_D$ = +75.1° (c = 0.011 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.33–7.24 (m, 4H), 7.22 (d, *J* = 7.6 Hz, 1H), 3.93 (d, *J* = 16.2 Hz, 1H), 3.66 (d, *J* = 16.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.1, 135.3, 134.6, 133.5, 130.2, 129.5, 128.7, 128.1, 127.9, 126.9, 124.4, 118.8 (qt, *J* = 287, 35.8 Hz), 111.3 (tq, *J* = 264, 35.6 Hz), 83.8 (t, *J* = 24.9 Hz), 31.4;

^{19}F NMR (471 MHZ, $CDCl_3$) δ −76.8 (s), −120.1, 121.5 (ABq, J_{AB} = 280.0 Hz);

IR (neat) 1740, 1451, 1219, 1190, 1151, 1116, 1076, 745, 731, 716 cm^{-1};

HRMS (ESI^+) calcd for $C_{17}H_{12}O_2F_5$ as $[M+H]^+$, 343. 0575. Found 343. 0761.

(*S*)-3-(perfluoropropyl)-3-phenylisochroman-1-one (3f)

30.2 mg, 77% yield; 90% ee;

$[\alpha]^{20}_D$ = +107.3° (c = 0.015 g/ml, $CHCl_3$);

^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.33 – 7.25 (m, 5H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.95 (d, *J* = 16.2 Hz, 1H), 3.67 (d, *J* = 16.2 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0, 135.2, 134.6, 133.5, 130.2, 129.4, 128.6, 128.1, 127.9, 127.1, 124.4, 118.8 (m), 116.3 (m), 113.9 (m), 111.9 (m), 109.9 (m), 107.8 (m), 84.7 (t, *J* = 25.3 Hz), 31.7;

^{19}F NMR (471 MHz, $CDCl_3$) δ −79.9 (t, *J* = 11.3 Hz, 3F), −116.1 – −118.4 (m, 2F), −120.5 (ddd, *J* = 289.6, 12.5, 4.7 Hz, 1F), −122.9 (ddd, *J* = 289.2, 12.5, 3.0 Hz, 1F);

IR (neat) 1741, 1461, 1450, 1340, 1226, 1125, 1074, 745, 730, 716, cm^{-1};

HRMS (ESI^+) calcd for $C_{18}H_{12}O_2F_7$ as $[M+H]^+$, 393. 0726. Found 393. 0718.

(*S*)-6-chloro-3-phenyl-3-(trifluoromethyl)isochroman-1-one (3j)

18.6 mg, 57% yield; 90% ee;

$[\alpha]^{20}_D$ = +112.9° (c = 0.018 g/ml, $CHCl_3$);

^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 1H), 7.54 – 7.50 (m, 3H), 7.40–7.33 (m, 3H), 7.32 – 7.29 (m, 2H), 3.83 (d, *J* = 16.4, 1H), 3.68 (d, *J* = 16.4 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 141.1, 137.0, 133.1, 131.9, 129.7, 128.9, 128.7, 127.9, 126.9, 122.8, 123.1 (d, *J* = 282 Hz), 83.2 (d, *J* = 30.6 Hz), 31.0;

^{19}F NMR (471 MHz, Chloroform-*d*) δ −78.7 (s);

IR (neat) 1736, 1600, 1270, 1185, 1168, 1095, 1074, 765, 720, 683 cm^{-1};

HRMS (ESI^+) calcd for $C_{16}H_{11}O_2F_3Cl$ as $[M+H]^+$, 327. 0400. Found 327.0397.

(*S*)-3,6-diphenyl-3-(trifluoromethyl)isochroman-1-one(3k)

24.3 mg, 66% yield; 77% ee;

$[\alpha]^{20}_D$ = +93.1° (c = 0.019 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.50 (m, 4H), 7.48 – 7.40 (m, 4H), 7.36 – 7.28 (d, *J* = 7.4 Hz, 3H), 3.89 (d, *J* = 16.2 Hz, 1H), 3.75 (d, *J* = 16.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): 162.3, 147.4, 139.1, 135.8, 133.5, 130.9, 129.6, 129.1, 128.8, 128.7, 127.2, 127.0, 126.9, 126.3, 123.3 (d, *J* = 282 Hz), 123.0, 83.2 (d, *J* = 30.4 Hz), 31.3;

^{19}F NMR (471 MHz, $CDCl_3$) δ −78.7 (s);

IR (neat) 2923, 1737, 1611, 1450, 1271, 1238, 1169, 1130, 1073, 758, 740, 721, 695 cm^{-1};

HRMS (ESI^+) calcd for $C_{22}H_{16}O_2F_3$ as $[M+H]^+$, 369.1102. Found 369.1100.

(*S*)-3-(4-fluorophenyl)-6-phenyl-3-(trifluoromethyl)isochroman-1-one (3l)

27.5 mg, 71% yield; 93% ee;

$[\alpha]^{20}_D$ = +103.5° (c = 0.014 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.51 (m, 5H), 7.49 – 7.39 (m, 4H), 7.02 (t, *J* = 8.6 Hz, 2H), 3.89 (d, *J* = 16.3 Hz, 1H), 3.70 (d, *J* = 16.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2 (d, *J* = 249 Hz), 162.1, 147.6, 139.0, 135.6, 131.0, 129.4 (d, *J* = 3.3 Hz), 129.2 (d, *J* = 8.7 Hz), 129.1, 128.8, 127.3, 127.0, 126.3, 123.1 (d, *J* = 282 Hz), 122.8, 116.0 (d, *J* = 21.7 Hz), 82.8 (d, *J* = 30.5 Hz), 31.3;

^{19}F NMR (471 MHz, $CDCl_3$) δ −78.9 (s), −110.5 (tt, *J* = 8.4, 5.0 Hz);

IR (neat) 1739, 1611, 1512, 1239, 1171, 1073, 988, 836, 745, 697 cm^{-1};

HRMS (ESI^+) calcd for $C_{22}H_{15}O_2F_4$ as $[M+H]^+$, 387.1008. Found 387.1002.

(*S*)-3,7-diphenyl-3-(trifluoromethyl)isochroman-1-one (3m)

29.8 mg, 81% yield; 86% ee;

$[\alpha]^{20}_D$ = +118.0° (c = 0.028 g/ml, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 1.9 Hz, 1H), 7.72 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.58 – 7.48 (m, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.28 (m, 5H), 3.86 (d, *J* = 16.3 Hz, 1H), 3.73 (d, *J* = 16.3 Hz, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 141.3, 138.9, 134.0, 133.5, 133.1, 129.6, 129.0, 128.8, 128.7, 128.4, 128.1, 127.1, 126.9, 124.7, 123.3 (d, *J* = 282 Hz), 83.0 (d, *J* = 30.4 Hz), 30.8;

^{19}F NMR (471 MHz, $CDCl_3$) δ −78.8 (s);

IR (neat) 2924, 1742, 1451, 1306, 1221, 1169, 1073, 760, 745, 702 cm^{-1};

HRMS (ESI$^+$) calcd for $C_{22}H_{16}O_2F_3$ as $[M+H]^+$, 369.1102. Found 369.1100.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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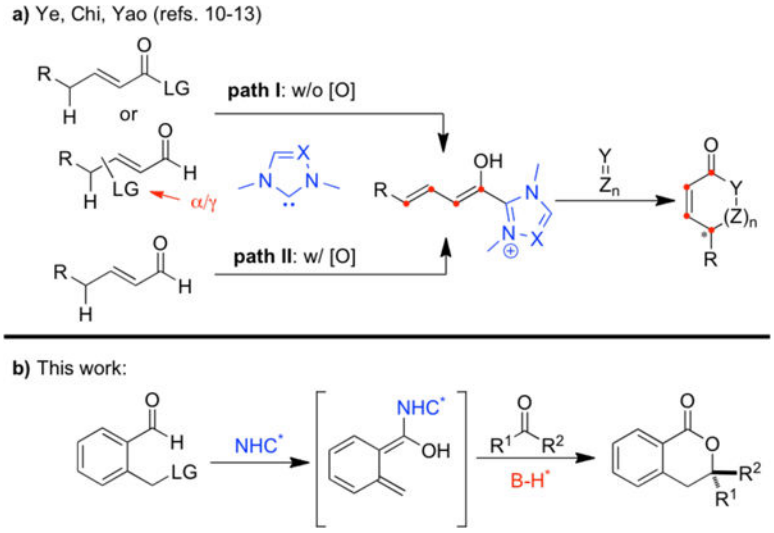
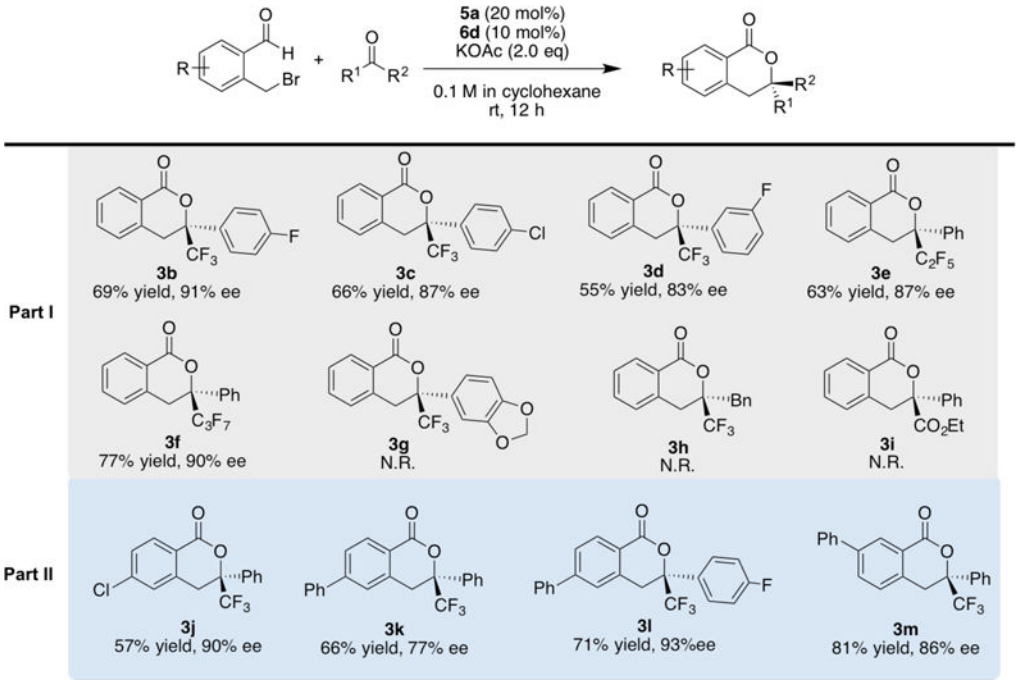
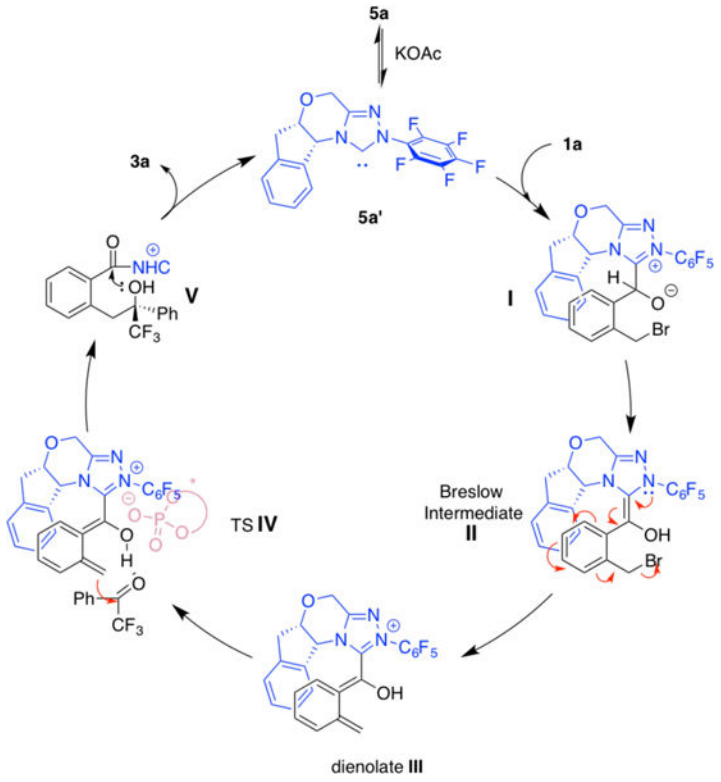


Scheme 1.

Pathways to dienolate intermediate through NHC catalysis



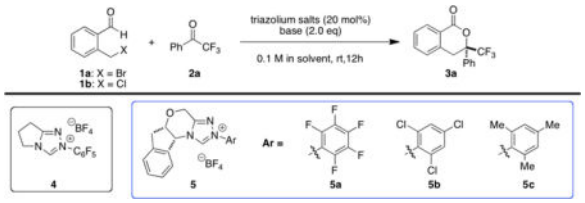
Scheme 2.
Substrate Scope



Scheme 3.
Proposed catalytic cycle

Table 1

NHC catalyst examination and reaction optimization



entry	Cat.	Solvent	Base	yield (%)[a]	ee
1	**4**	THF	K_2CO_3	57	NA
2	**5a**	THF	K_2CO_3	76	45
3	**5b**	THF	K_2CO_3	42	24
4	**5c**	THF	K_2CO_3	N.R.	NA
5	**5a**	n-hexane	KOAc	64	63
6	**5a**	cyclohexane	KOAc	**61**	**76**
7[c]	**5a**	cyclohexane	KOAc	21	59

Standard Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), **5a** (20 mol%, 0.020 mmol) and base (0.20 mmol) in 1.0 mL of anhydrous solvent, under argon, 23° C, for 12h.

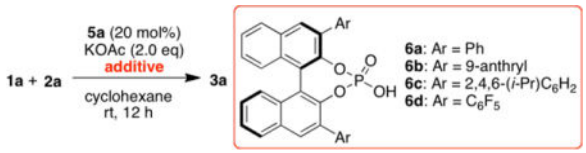
[a] Isolated yield.

[b] Determined by HPLC on a chiral stationary phase.

[c] **1b** was used instead of **1a**.

Table 2

Additive Effect



entry	additive	yield (%)[a]	ee (%)[b]
1	3Å MS	42	78
2	4Å MS	58	77
3	5Å MS	53	77
4	LiCl (1.0 eq)	52	77
5	$Sc(OTf)_3$ (10 mol%)	55	71
6	**6a** (20 mol%)	66	82
7	**6b** (20 mol%)	63	84
8	**6c** (20 mol%)	56	74
9	**6d** (20 mol%)	51	95
10	**6d** (10 mol%)	**68**	**95**
11[c]	**6d** (20 mol%)	64	−84

Conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), **5a** (20 mol%, 0.020 mmol) and KOAc (0.20 mmol) in 1.0 mL of anhydrous cyclohexane, under argon, 23° C, for 12h.

a–b See Table 1.

c ***ent*- 5a** was used instead of **5a**.