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NUCLEOPHILIC ADDITION TO *N*-BENZOYLISOQUINOLINIUM CATION CATALYZED BY SODIUM TETRACYANOCYCLOPENTADIENIDES

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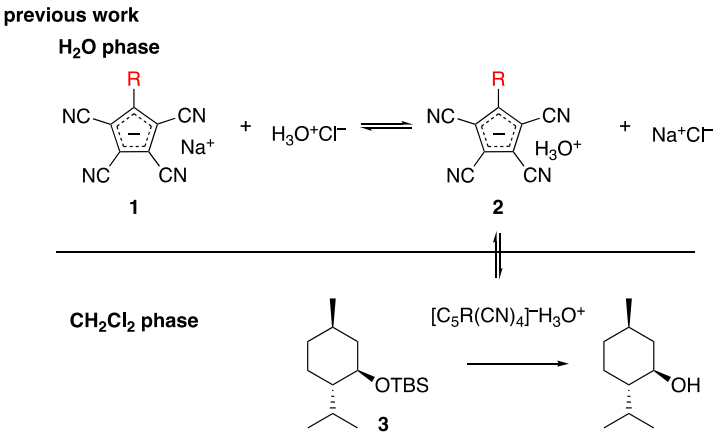
Abstract – Tetracyanocyclopentadienide-catalyzed nucleophilic addition to an *N*-benzoylisoquinolinium cation is reported. The reaction is accelerated by the *in situ* formation of the soluble lipophilic salt of an *N*-benzoylisoquinolinium cation and a tetracyanocyclopentadienide anion.

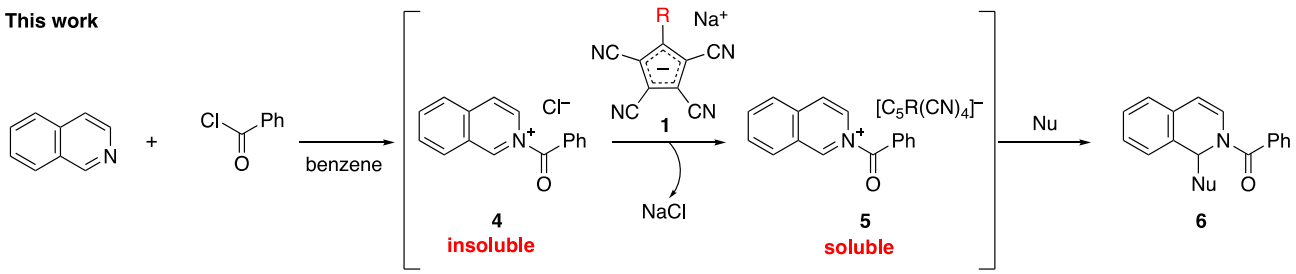
Salts of superacids serve as useful reagents and catalysts in a variety of organic reactions. Tetracyanocyclopentadienide is a superacid anion that is stabilized by the aromaticity of the cyclopentadienide ring and the electron-withdrawing effect of the four cyano groups.[1] Although 50 years have lapsed since the discovery of tetra- and pentacyanocyclopentadienides by Webster,[2] there are very few reports on the use of these compounds as catalysts. We previously established the efficient synthesis of sodium tetracyanocyclopentadienides ($Na[C_5R(CN)_4]$) from tetracyanothiophene and sulfones.[3] The substituent R on the cyclopentadienide ring of the $C_5R(CN)_4$ anion could be directly transformed into other functional groups by a variety of reactions. Recently, we reported the catalytic activity of tetracyanocyclopentadienides, where a tetracyanocyclopentadienide pyridinium salt catalyzed the methanolysis of the ethylene glycol acetals of aromatic aldehydes.[4] We then became interested in an anionic phase-transfer reaction using $C_5R(CN)_4$ anions as the catalyst. The formation of a lipophilic ion pair comprising a reactive cation and a stable anion is the key step in accelerating this reaction.[5] Chiral phosphates and carboxylates have been reported for use as anionic phase-transfer catalysts in the catalytic desymmetrization of aziridinium salts and catalytic asymmetric halogenation with quaternary *N*-haloammonium cations.[6] We considered that a lipophilic superacid anion would be suitable as an anionic phase-transfer catalyst, which increases the solubility of cations in an organic solvent while imparting high stability to the reactive species.

Despite their ionic nature, sodium tetracyanocyclopentadienides **1** are highly lipophilic and can be extracted with ethyl acetate from an aqueous solution. Sodium salt **1** transfers a hydronium cation to a

CH_2Cl_2 phase by forming an amphipathic ion pair **2** and catalyzes the hydrolysis of **3** to L-menthol in an aqueous HCl–CH_2Cl_2 biphasic system (Scheme 1).[7] The catalytic activity of **1** is correlated to the hydrophobicity of the substituent R on the cyclopentadienide ring. The hydrolysis is well accelerated when R is a CO_2-menthyl group but is slow when the hydrophilic tetracyanocyclopentadienide with R = CO_2Et is employed. In this report, we have focused on *N*-benzoylisoquinolinium salt **4**, which is prepared from isoquinoline and benzoyl chloride and is highly reactive to various nucleophiles (Scheme 2). In the past, catalytic nucleophilic additions to *N*-acylquinolinium or *N*-acylisoquinolinium salts were mainly achieved using Brønsted or Lewis acid catalysts, or anion binding catalysts.[8] However, there are only a few reports on the use of anionic phase-transfer catalysts in these reaction systems. In the presence of tetracyanocyclopentadienide **1**, salt **4** could form a lipophilic ion pair **5**, which could be subjected to nucleophilic addition. We herein report a unique catalytic reaction in which tetracyanocyclopentadienides enhance the solubility of a reactive *N*-benzoylisoquinolinium cation intermediate.

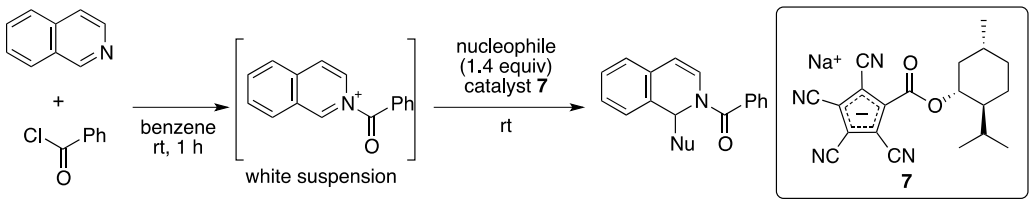


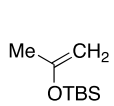
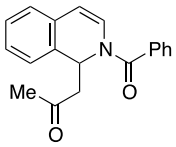
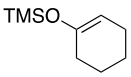
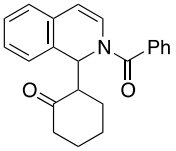
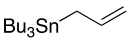
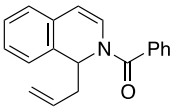
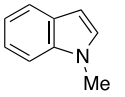
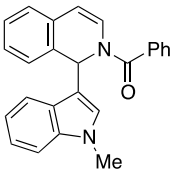
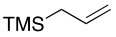
Scheme 1. Tetracyanocyclopentadienide as a solubility enhancer for the hydronium cation



Scheme 2. Tetracyanocyclopentadienide (R = hydrophobic group) as a solubility enhancer for the *N*-benzoylisoquinolinium cation

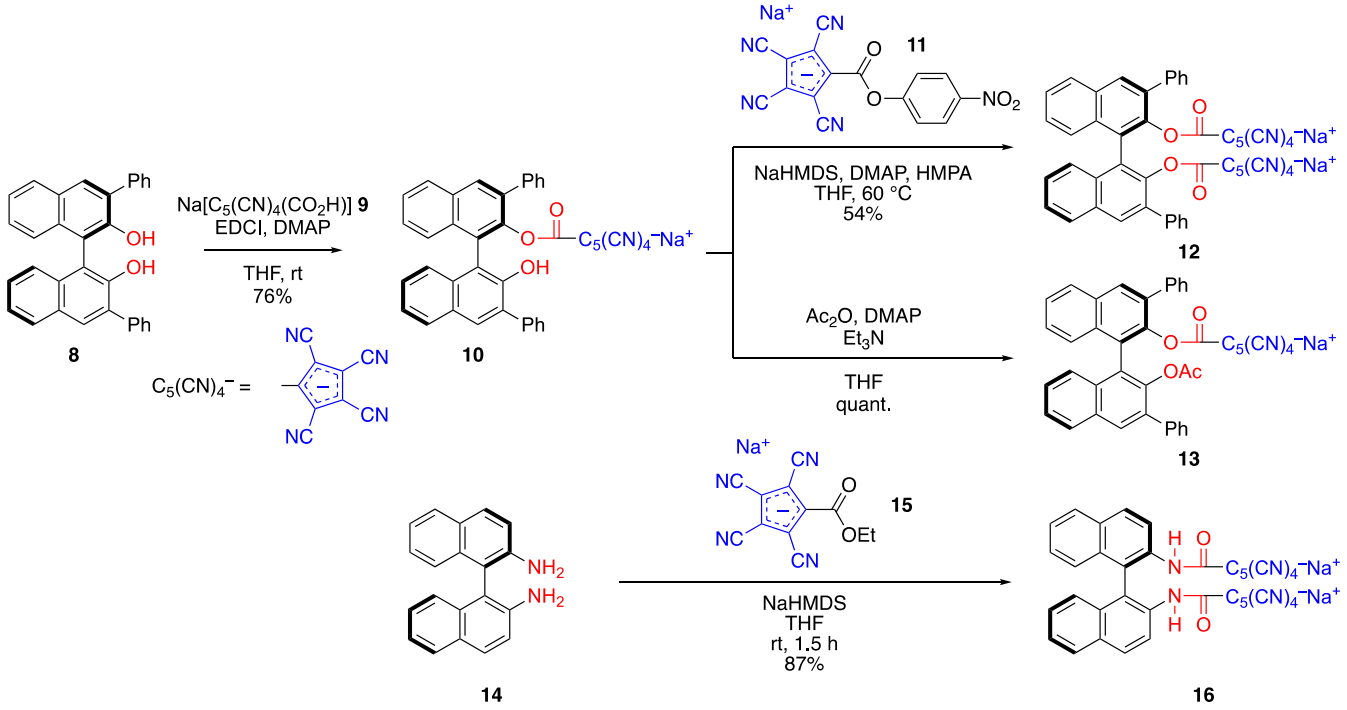
Table 1. Catalytic activity of tetracyanocyclopentadienide as a solubility enhancer for a reactive cation



entry	nucleophile	catalyst **7**	product[a]	result
1		2.0 mol%	 **6a**	18 h, 95%
2		–		27 h, 0%
3		1.3 mol%	 **6b**	8 h, 89% (55:45 dr)
4		–		24 h, 0%
5		1.3 mol%	 **6c**	4 h, 87%
6		–		24 h, 91%
7		1.3 mol%	 **6d**	4 h, 66%
8		–		3 h, 85%
9		1.3 mol%	–	24 h, no adduct

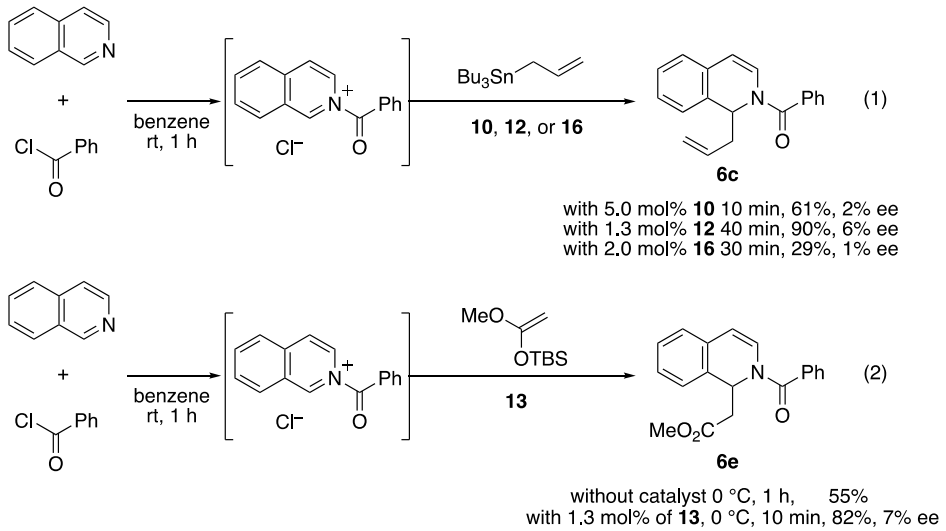
[a] No optical rotation was observed for adducts **6a**-**6d** in the reactions with use of catalyst **7**.

Acylisoquinolinium salts are soluble in dichloromethane and undergo nucleophilic addition without a catalyst.[9] In benzene, the reaction of isoquinoline with benzoyl chloride provided a white suspension of *N*-benzoylisoquinolinium chloride. Thus, the catalytic reactivity of tetracyanocyclopentadienide for nucleophilic addition to a *N*-benzoylisoquinolinium salt was examined in a benzene solution (Table 1). The nucleophilic addition of acetone enol *tert*-butyldimethylsilyl ether using 2.0 mol% of tetracyanocyclopentadienide **7** proceeded to completion after 18 h to afford **6a** in good yield. In the absence of catalyst **7**, the reaction did not progress even after 27 h (entries 1 and 2). The reactions of *N*-benzoylisoquinolinium chloride with cyclohexanone enol trimethylsilyl ether and allyltributylstannane were also accelerated in the presence of a catalytic amount of **7** to give **6b** and **6c**, respectively (entries 3-6). The reaction with *N*-methylindole afforded the addition product with and without **7**, possibly because *N*-methylindole had sufficient polarity to enhance the solubility of *N*-acylisoquinolinium chloride (entries 7 and 8). The allyl product was not obtained when using allyltrimethylsilane, which is a weaker nucleophile than allylstannane (entry 9); instead, benzoic anhydride was obtained upon quenching the reaction with water.



Scheme 3. Synthesis of tetracyanocyclopentadienides with binaphthyl-type chiral auxiliaries

We next examined the nucleophilic addition using tetracyanocyclopentadienides attached to a binaphthyl-type chiral auxiliary. 3,3′-Diphenyl-BINOL **8** was subjected to 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) condensation with (tetracyanocyclopentadienyl)carboxylic acid **9** to give monoester **10** in good yield.[10] The second tetracyanocyclopentadienide ester was introduced into **10** with *p*-nitrophenyl ester **11** by the mediation of NaHMDS in THF–HMPA, affording diester-type catalyst **12**. Acetylation of the phenolic hydroxy group of **10** provided compound **13** in quantitative yield. (*R*)-2,2'-Diamino-1,1'-binaphthyl (BINAM) (**14**) and ethyl ester **15** were condensed with NaHMDS to afford diamide-type catalyst **16** in good yield (Scheme 3).

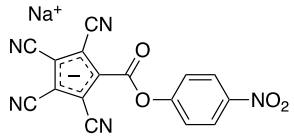


Allylation with allyltributylstannane was then explored using catalysts **10** and **12** (eq. 1). In both cases, the reaction proceeded to completion within 40 min. A small degree of enantioselectivity was observed with diester-type catalyst **12**. While, the product yield was significantly decreased with use of diamide-type catalyst **16**, possibly due to low solubility of *N*-benzoylisoquinilinium salt formed by salt exchange with **16**. An acyl-Mannich reaction with a ketene silyl acetal gave adduct **6e** in moderate yield in the absence of the catalyst. When 1.3 mol% of **13** was used, the reaction was completed within 10 min at 0 °C to afford **6e** in good yield but with poor enantioselectivity (eq. 2). Under the condition at –80 °C in toluene, the acyl-Mannich reaction did not progressed. The nucleophilic addition of acetone enol *tert*-butyldimethylsilyl ether with BINOL-type catalysts **10** and **13** gave addition product **6a** with almost no enantioselectivity.

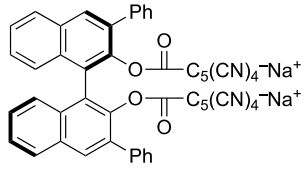
In conclusion, we have explored the unique properties of tetracyanocyclopentadienide derivatives and their potential use as catalysts for nucleophilic addition to *N*-benzoylisoquinolinium chloride. The sodium salt of $C_5R(CN)_4$ was found to show high catalytic activity as a solubility enhancer for the reactive cation. Slight asymmetric induction was observed in the preliminary experiments using the BINOL esters of this salt as asymmetric catalysts for allylation or acyl-Mannich reaction. Studies aimed at improving the enantioselectivity and further extending the applications of tetracyanocyclopentadienides are in progress in our laboratory.

EXPERIMENTAL

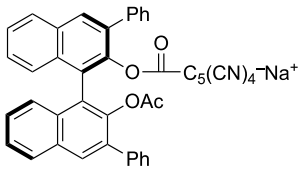
General Information. All air- and moisture-sensitive reactions were carried out under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions. Throughout the experimental methods described herein, the term "dried" refers to the drying of an organic solution over $MgSO_4$ followed by filtration. Flash chromatography was carried out using silica gel (spherical, neutral, particle size 40−50 mm). Melting points are uncorrected. Chemical shifts are reported in ppm relative to the solvent signal (δ 1.94 ppm for CD_3CN) or internal TMS (δ 0.00 ppm for $CDCl_3$) for ^1H NMR spectra and to the solvent signals (δ 1.39 ppm for CD_3CN, δ 77.0 ppm for $CDCl_3$) for ^{13}C NMR spectra. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). High-resolution mass spectra were recorded on a magnetic sector FAB mass spectrometer, a magnetic sector EI mass spectrometer, or an orbitrap DART mass spectrometer.



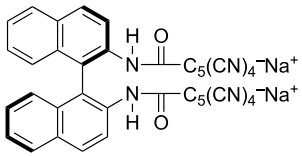
***p*-Nitorophenyl ester 11.** To a solution of $Na[C_5(CN)_4(CO_2H)]$ **9**[3] (1.50 g, 6.46 mmol, 1.0 equiv), DMAP (320 mg, 2.58 mmol, 0.40 equiv), and *p*-nitrophenol (2.70 g, 19.3 mmol, 3.0 equiv) in THF (130 mL) was added EDCI (2.50 g, 12.9 mmol, 2.0 equiv), and the reaction mixture was stirred at room temperature for 3.0 h. The reaction was quenched with 10% aqueous HCl solution, and the resulting mixture was extracted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and concentrated under reduced pressure. Flash chromatography (15% MeCN in Et_2O) afforded nitrophenyl ester **11** (1.46 g, 64%) as a beiges solid. Mp 320–326 °C (decomp.); IR (KBr) 2236, 2221, 1737, 1521, 1467, 1361, 1246, 1220, 1089 cm^{-1}; ^1H NMR (CD_3CN, 600 MHz) δ 8.30 (2H, AA′BB′, J_{AB} = 9.2 Hz, J_{AB}' = 0 Hz, J_{AA}' = 2.7 Hz, J_{BB}' = 2.7 Hz), 7.53 (2H, AA′BB′, J_{AB} = 9.2 Hz, J_{AB}' = 0 Hz, J_{AA}' = 2.7 Hz, J_{BB}' = 2.7 Hz); ^{13}C NMR (CD_3CN, 150 MHz) δ 159.5, 156.5, 146.5, 126.3, 123.7, 121.6, 115.6, 114.9, 104.6, 102.3; HRFABMS *m/z* $[M–Na]^-$ calcd for $C_{16}H_4O_4N_5$ 330.0263, found 330.0250.



Diester 12. To a solution of monoester **10**[10] (710 mg, 1.09 mmol, 1.0 equiv), *p*-nitrophenyl ester **11** (1.15 g, 3.3 mmol, 3.0 equiv), DMAP (30 mg, 0.25 mmol, 0.2 equiv) in THF–HMPA (9:1 mixture, 10 mL) at room temperature was added NaHMDS (1.09 M solution in THF, 2.5 mL, 2.72 mmol, 2.5 equiv), and the reaction mixture was stirred at 60 °C for 20 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (twice, 20% MeCN in Et_2O and 0→8% MeCN in EtOAc) afforded diester **12** (514 mg, 54%) as a beiges solid. Mp 345–350 °C (decomp.); $[\alpha]^{25}_D$ –253.6 (*c* 1.00, MeCN); IR (KBr) 2223, 1710, 1619, 1477, 1239, 1088 cm^{-1}; ^1H NMR (600 MHz, CD_3CN, 64 °C) δ 8.06 (2H, s), 7.96 (2H, d, *J* = 6.1 Hz), 7.80–7.76 (4H, m), 7.49–7.44 (2H, m), 7.40–7.30 (10H, m); ^{13}C NMR (150 MHz, CD_3CN, 64 °C) δ 159.7, 146.6, 139.5, 136.9, 133.8, 133.2, 130.9, 130.7, 129.4, 129.1, 128.6, 127.7, 127.4, 127.3, 126.7, 122.1, 115.2, 115.0, 104.1, 101.5; HRFABMS *m/z* $[M–Na]^-$ calcd for $C_{52}H_{20}O_4N_8Na$ 843.1505, found 843.1480.

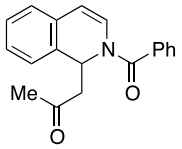


Acetate 13. To a solution of ester **10**[10] (30 mg, 0.046 mmol, 1.0 equiv) in THF (0.5 mL) were added Et_3N (32 μL, 0.23 mmol, 5.0 equiv), acetic anhydride (13 μL, 0.14 mmol, 3.0 equiv), and DMAP (0.6 mg, 0.005 mmol, 0.1 equiv), and the reaction mixture was stirred at room temperature for 14 h. After concentration, saturated aqueous NH_4Cl solution was added to the residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (5→30% MeCN in EtOAc) afforded **13** (32 mg, quant.) as a pale yellow solid. Mp 260-265 ºC; $[\alpha]^{24}_D$ –50.8 (*c* 1.00, MeOH); IR (KBr) 3056, 2925, 2221, 1717, 1475, 1235, 1178, 1088 cm^{-1}; 53:47 ratio of rotamers; ^1H NMR (600 MHz, CD_3CN) δ 8.22 (0.5H, s), 8.21 (0.5H, s), 8.11–8.06 (1.5H, m), 8.08 (1H, s), 8.00 (0.5H, d, *J* = 8.3 Hz), 7.82 (1H, d, *J* = 7.3 Hz), 7.77 (1H, d, *J* = 7.5 Hz), 7.73 (1H, d, *J* = 7.2 Hz), 7.58–7.54 (1.5H, m), 7.53–7.50 (1.5H, m), 7.48–7.44 (2H, m), 7.43–7.32 (5H, m), 7.21 (1H, d, *J* = 7.2 Hz), 7.18 (1H, d, *J* = 8.4 Hz), 7.12 (1H, d, *J* = 8.6 Hz), 1.64 (1.5H, s), 1.54 (1.5H, s); ^{13}C NMR (150 MHz, CD_3CN) δ 169.6 (C), 169.5 (C), 159.3 (C x 2), 146.1 (C), 145.9 (C), 145.63 (C), 145.57 (C), 138.8 (C), 138.5 (C), 135.8 (C), 135.6 (C), 134.1 (C), 133.7 (C), 133.5 (C), 133.4 (C), 133.03 (C), 133.01 (C), 132.9 (C), 132.8 (C), 131.4 (CH), 131.2 (CHx2), 131.1 (CH), 130.4 (CH), 130.2 (CH), 130.01 (CH), 129.99 (CH), 120.6 (CH), 129.4 (CHx2), 129.35 (CHx2), 129.30 (CHx2), 129.2 (CH), 128.8 (CH), 128.74 (CH), 128.67 (CH), 128.0 (CH), 127.6 (CHx4), 127.30 (CHx2), 127.27 (CHx2), 127.1 (CHx2), 126.82 (CH), 126.78 (CH), 129.8 (Cx4), 126.2 (C), 126.1 (C), 126.6 (C), 126.0 (C), 121.2 (Cx2), 115.3 (C), 115.2 (C), 114.8 (Cx2), 104.2 (C), 103.9 (C), 101.7 (Cx2); 20.6 (CH_3 x 2); HRDARTMS *m/z* $[M–Na]^–$ calcd for $C_{44}H_{23}O_4N_4$ 671.1725, found 671.1727.

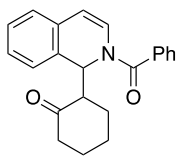


Diamide 16. To a solution of (*R*)- 2,2'-diamino-1,1'-binaphthyl (BINAM; **14**) (120 mg, 0.422 mmol, 1.0 equiv) in THF (2.5 mL) was added NaHMDS solution (1.09 M in THF, 2.0 mL, 2.23 mmol, 5.3 equiv) at room temperature. After 1 h, a solution of $Na[C_5(CN)_4(CO_2Et)]$ **15**[3] (300 mg, 1.15 mmol l, 2.7 equiv) in THF (2.5 mL) was added *via* cannula, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with 2 M aqueous HCl solution, and the mixture was alkalized with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (30→50% MeCN in CH_2Cl_2) afforded

16 (263 mg, 87%) as a pale yellow solid. Mp 345–348 °C; $[\alpha]^{24}_{D}$ +54.7 (*c* 0.49, MeOH); IR (KBr) 2219, 1652, 1499, 1276 cm^{-1}; ^{1}H NMR (600 MHz, CD_3CN) δ 8.37 (2H, d, *J* = 9.0 Hz), 8.09 (2H, d, *J* = 9.0 Hz), 7.95 (2H, d, *J* = 7.7 Hz), 7.95 (2H, br s), 7.41 (2H, dd, *J* = 7.7, 7.2 Hz), 7.25 (2H, dd, *J* = 8.3, 7.2 Hz), 7.04 (2H, d, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, CD_3CN) δ 160.8, 136.3, 133.6, 132.7, 130.5, 129.2, 128.6, 128.1, 126.6, 125.9, 124.0, 123.4, 115.8, 115.0, 103.2, 98.6; HRFABMS *m/z* $[M–Na]^-$ calcd for $C_{40}H_{14}O_2N_{10}Na$ 689.1199, found 689.1219.

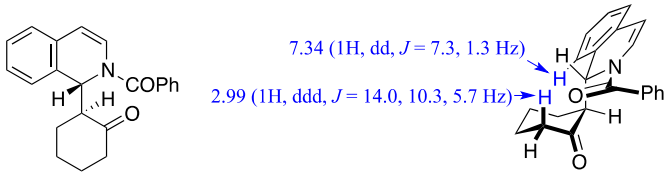


1-(2-Benzoyl-1,2-dihydroisoquinolin-1-yl)propan-2-one (6a) (Table 1, entry 1). To a solution of isoquinoline (0.118 mL, 129 mg, 1.0 mmol, 1.0 equiv) in benzene (2 mL) was added benzoyl chloride (0.116 mL, 140 mg, 1.0 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 1 h. $Na[C_5(CN)_4(CO_2Menthyl)]$ **7**[3] (7.4 mg, 0.02 mmol, 0.02 equiv) was added to the resulting suspension, and a solution of 2-((*tert*-butyldimethylsilyl)oxy)-1-propene (241 mg, 1.4 mmol, 1.4 equiv) in benzene (1 mL) was transferred to the reaction mixture *via* cannula. After stirring at room temperature for 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (50% EtOAc in *n*-hexane) afforded **6a** (275 mg, 95%) as a pale yellow oil. IR (film) 3061, 1715, 1655, 1623, 1356 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52–7.50 (2H, m), 7.48 (1H, ddt, *J* = 8.8, 6.4, 1.3 Hz), 7.44–7.41 (2H, m), 7.32 (1H, dd, *J* = 7.5, 1.5 Hz), 7.26 (1H, td, *J* = 7.5, 1.5 Hz), 7.23 (1H, td, *J* = 7.5, 1.5 Hz), 7.12 (1H, dd, *J* = 7.5, 1.5 Hz), 6.48 (1H, d, *J* = 5.7 Hz), 6.20 (1H, dd, *J* = 7.3, 6.4 Hz), 5.89 (1H, d, *J* = 5.7 Hz), 2.89 (1H, dd, *J* = 14.3, 7.3 Hz), 2.76 (1H, dd, *J* = 14.3, 6.4 Hz), 2.19 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.7, 169.1, 134.0, 132.1, 130.9, 129.9, 128.7, 128.4, 128.1, 127.5, 126.8, 126.6, 124.9, 109.5, 51.0, 48.0, 30.6; HREIMS *m/z* M^+ calcd for $C_{19}H_{17}O_2N$ 291.1259, found 291.1254.

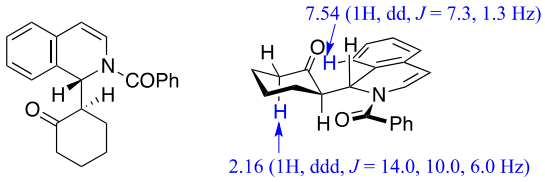


2-(2-Benzoyl-1,2-dihydroisoquinolin-1-yl)cyclohexan-1-one (6b) (Table 1, entry 3). To a solution of isoquinoline (0.118 mL, 129 mg, 1.0 mmol, 1.0 equiv) in benzene (2 mL) was added benzoyl chloride (0.116 mL, 140 mg, 1.0 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 1 h. $Na[C_5(CN)_4(CO_2Menthyl)]$ **7**[3] (7.4 mg, 0.02 mmol, 0.02 equiv) was added to the resulting suspension,

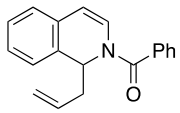
and 1-(trimethylsilyloxy)cyclohexene (0.268 mL, 1.4 mmol, 1.4 equiv) was added. After stirring at room temperature for 8 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (30% EtOAc in *n*-hexane) afforded **6b** (294 mg, 89%, dr = 55:45) as a pale yellow oil. For analytical samples, the diastereomers were separated by flash chromatography (0→2% EtOAc in CH_2Cl_2).



Major isomer: R_f = 0.43 (4% EtOAc in CH_2Cl_2); IR (film) 2937, 1703, 1658, 1622, 1358 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46–7.43 (3H, m), 7.41–7.38 (2H, m), 7.34 (1H, dd, *J* = 7.3, 1.3 Hz), 7.28 (1H, td, *J* = 7.3, 1.3 Hz), 7.25 (1H, td, *J* = 7.3, 1.3 Hz), 7.12 (1H, dd, *J* = 7.3, 1.3 Hz), 6.49 (1H, d, *J* = 7.4 Hz), 6.34 (1H, d, *J* = 8.1 Hz), 5.87 (1H, d, *J* = 7.4 Hz), 2.99 (1H, ddd, *J* = 14.0, 10.3, 5.7 Hz), 2.76 (1H, td, *J* = 8.1, 6.2 Hz), 2.39 (1H, dt, *J* = 14.0, 4.8 Hz), 1.97–1.90 (2H, m), 1.78–1.64 (3H, m), 1.53 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.5, 169.2, 134.3, 130.5, 130.4, 129.7, 128.3, 128.2, 128.0, 127.8, 127.1, 126.9, 124.9, 109.9, 52.8, 52.3, 40.4, 27.6, 26.6, 21.6; HREIMS *m/z* M^+ calcd for $C_{22}H_{21}O_2N$ 331.1572, found 331.1560.

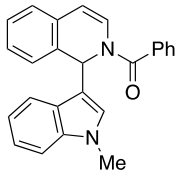


Minor isomer: R_f = 0.53 (4% EtOAc in CH_2Cl_2); IR (film) 2939, 1708, 1655, 1619, 1362 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (1H, dd, *J* = 7.3, 1.3 Hz), 7.49–7.45 (3H, m), 7.42–7.39 (2H, m), 7.23 (1H, td, *J* = 7.3, 1.3 Hz), 7.20 (1H, td, *J* = 7.3, 1.5 Hz), 7.10 (1H, dd, *J* = 7.3, 1.3 Hz), 6.44 (1H, d, *J* = 5.1 Hz), 6.37 (1H, d, *J* = 10.4 Hz), 5.97 (1H, d, *J* = 5.1 Hz), 2.79 (1H, td, *J* = 10.4, 5.3 Hz), 2.38 (1H, dt, *J* = 14.0, 4.0 Hz), 2.16 (1H, ddd, *J* = 14.0, 10.0, 6.0 Hz), 2.00–1.92 (3H, m), 1.83 (1H, m), 1.72 (1H, m), 1.58 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.2, 169.1, 134.4, 133.3, 130.7, 129.7, 128.6, 128.3, 128.0, 127.6, 127.3, 126.7, 124.6, 111.6, 54.3, 51.6, 43.0, 32.3, 28.3, 25.0; HREIMS *m/z* M^+ calcd for $C_{22}H_{21}O_2N$ 331.1572, found 331.1559.



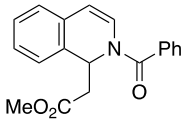
1-Allyl-2-benzoyl-1,2-dihydroisoquinoline (6c) (Table 1, entry 5). To a solution of isoquinoline (0.118 mL, 129 mg, 1.0 mmol, 1.0 equiv) in benzene (2 mL) was added benzoyl chloride (0.116 mL, 140 mg, 1.0 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 1 h. $Na[C_5(CN)_4(CO_2Menthyl)]$ **7**[3] (5.0 mg, 0.013 mmol, 0.013 equiv) was added to the resulting suspension, and allyltributyltin (0.434 mL, 1.4 mmol, 1.4 equiv) was added. After 4 h, the reaction was quenched with 10% aqueous KF solution, and the resulting mixture was extracted with EtOAc, washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (30% EtOAc in *n*-hexane) afforded **6c** (241 mg, 87%) as a pale yellow oil. IR (film) 3071, 1659, 1622, 1355 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50–7.47 (2H, m), 7.47 (1H, m), 7.43–7.41 (2H, m), 7.26–7.20 (2H, m), 7.15 (1H, d, *J* = 7.0 Hz), 7.10 (1H, d, *J* = 7.0 Hz), 6.44 (1H, d, *J* = 7.5 Hz), 5.88–5.80 (3H, m), 5.03 (1H, d, *J* = 10.3 Hz), 4.97 (1H, d, *J* = 17.1 Hz), 2.54–2.47 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.1, 134.7, 134.2, 132.7, 130.5, 130.1, 128.44, 128.38, 127.7, 127.1, 126.7, 126.6, 124.7, 117.7, 109.6, 54.1, 39.4; HREIMS *m/z* M^+ calcd for $C_{19}H_{17}ON$ 275.1310, found 275.1308.

When diester **12** (11.3 mg, 0.013 mmol) was used as a catalyst instead of **7**, allylation product **6c** (248 mg, 90%) was obtained with 6% ee determined by HPLC (CHIRALCEL OD-3, 1% *i*-PrOH in *n*-hexane, 254 nm, 1.0 mL/min). $[\alpha]^{25}_D$ +27.7 (*c* 2.03, $CHCl_3$).



2-Benzoyl-1-(1-methyl-1*H*-indol-3-yl)-1,2-dihydroisoquinoline (6d) (Table 1, entry 8). To a solution of isoquinoline (0.118 mL, 129 mg, 1.0 mmol, 1.0 equiv) in benzene (10 mL) was added benzoyl chloride (0.116 mL, 140 mg, 1.0 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 1 h. *N*-Methylindole (0.175 mL, 183 mg, 1.4 mmol, 1.4 equiv) was added. After 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and the resulting mixture was extracted with EtOAc, washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (20% EtOAc in *n*-hexane) afforded **6d** (259 mg, 85%) as a beiges solid. Mp 164–166 °C; IR (film) 3065, 3009, 1655, 1622, 1359 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 7.3 Hz), 7.49–7.44 (2H, m), 7.42 (1H, t, *J* = 7.3 Hz), 7.39–7.33 (2H, m), 7.33–7.17 (7H, m), 7.12 (1H, t, *J* = 6.6 Hz), 6.58 (1H, s), 6.38 (1H, d, *J* = 7.1 Hz), 6.00 (1H, d, *J* = 7.1 Hz), 3.62 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.9, 136.9, 135.0, 133.2,

130.5, 130.3, 129.5, 128.4, 128.2, 127.7, 127.5, 127.1, 126.9, 126.2, 124.7, 121.7, 120.7, 119.5, 115.3, 110.5, 109.0, 50.3, 32.7; HRDARTMS *m/z* $[M+H]^+$ calcd for $C_{25}H_{21}ON_2$ 365.1648, found 365.1648.



Methyl 2-(2-benzoyl-1,2-dihydroisoquinolin-1-yl)acetate (6e) (eq 2). To a solution of isoquinoline (0.118 mL, 129 mg, 1.0 mmol, 1.0 equiv) in benzene (2 mL) was added benzoyl chloride (0.116 mL, 140 mg, 1.0 mmol, 1.0 equiv), and the mixture was stirred at room temperature for 1 h. Catalyst **13** (9.0 mg, 0.013 mmol, 0.013 equiv) was added to the resulting suspension, and the mixture was cooled to 0 °C. 1-(*tert*-Butyldimethylsiloxy)-1-methoxyethene (0.306 mL, 1.4 mmol, 1.4 equiv) was added dropwise over 5 min. After 10 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with EtOAc, washed with brine, dried, and concentrated under reduced pressure. Flash chromatography (30% EtOAc in *n*-hexane) afforded **6e** (251 mg, 82%) as a pale yellow solid. Mp 98–100 °C (for racemic sample); $[\alpha]^{25}_D$ –12.5 (*c* 2.05, $CHCl_3$) for 7% ee determined by HPLC (CHIRALCEL OD-3, 10% *i*-PrOH in *n*-hexane, 254 nm, 1.0 mL/min); IR ($CHCl_3$) 3012, 2952, 1734, 1658, 1625, 1362 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54–7.51 (2H, m), 7.49 (1H, m), 7.45–7.41 (2H, m), 7.30–7.22 (3H, m), 7.12 (1H, d, *J* = 7.0 Hz), 6.49 (1H, d, *J* = 6.8 Hz), 6.18 (1H, dd, *J* = 7.2, 7.0 Hz), 5.90 (1H, d, *J* = 6.8 Hz), 3.68 (3H, s), 2.77 (1H, dd, *J* = 13.6, 7.2 Hz), 2.65 (1H, dd, *J* = 13.6, 7.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 169.1, 134.1, 131.7, 130.9, 130.0, 128.7, 128.4, 128.3, 127.5, 126.5 (x2), 124.9, 109.4, 51.9, 51.6, 38.9; HRDARTMS *m/z* $[M+H]^+$ calcd for $C_{19}H_{18}O_3N$ 308.1281, found 308.1283.

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REFERENCES

1. (a) O. W. Webster, *J. Am. Chem. Soc.*, 1966, **88**, 3046; (b) E. S. Stoyanov, K.-C. Kim, and C. A. Reed, *J. Am. Chem. Soc.*, 2006, **128**, 8500.
2. (a) O. W. Webster, *J. Am. Chem. Soc.*, 1965, **87**, 1820; (b) O. W. Webster, *J. Am. Chem. Soc.*, 1966, **88**, 4055; (c) H. E. Simmons, R. D. Vest, S. A. Vladuchick, and O. W. Webster, *J. Org. Chem.*, 1980, **45**, 5113.

3. T. Sakai, S. Seo, J. Matsuoka, and Y. Mori, *J. Org. Chem.*, 2013, **78**, 10978.
4. T. Sakai, Y. Nagao, Y. Nakamura, and Y. Mori, *ACS Omega*, 2017, **2**, 8543.
5. (a) H. Kobayashi, T. Sonoda, and H. Iwamoto, *Chem. Lett*., 1981, 579; (b) H. Iwamoto, H. Kobayashi, P. Murer, T. Sonoda, and H. Zollinger, *Bull. Chem. Soc. Jpn*., 1993, **66**, 2590; (c) J. Ichikawa, H. Kobayashi, and T. Sonoda, *J. Synth. Org. Chem. Jpn*., 1988, **46**, 943; (d) K. Brak and E. N. Jacobsen, *Angew. Chem. Int. Ed*., 2013, **52**, 534; (e) M. Mahlau and B. List, *Angew. Chem. Int. Ed*., 2013, **52**, 518; (f) D. Parmar, E. Sugiono, S. Raja, and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047.
6. (a) G. L. Hamilton, T. Kanai, and F. D. Toste, *J. Am. Chem. Soc*., 2008, **130**, 14984; (b) V. Rauniyar, A. D. Lackner, G. L. Hamilton, and F. D. Toste, *Science*, 2011, **334**, 1681; (c) R. J. Phipps, K. Hiramatsu, and F. D. Toste, *J. Am. Chem. Soc*., 2012, **134**, 8376; (d) T. Honjo, R. J. Phipps, V. Rauniyar, and F. D. Toste, *Angew. Chem. Int. Ed*., 2012, **51**, 9684; (e) R. J. Phipps and F. D. Toste, *J. Am. Chem. Soc*., 2013, **135**, 1268; (f) H. P. Shunatona, N. Früh, Y.-M. Wang, V. Rauniyar, and F. D. Toste, *Angew. Chem. Int. Ed*., 2013, **52**, 7724; (g) F. Romanov-Michailidis, L. Guénée, and A. Alexakis, *Angew. Chem. Int. Ed*., 2013, **52**, 9266; (h) W. Xie, G. Jiang, H. Liu, J. Hu, X. Pan, H. Zhang, X. Wan, Y. Lai, and D. Ma, *Angew. Chem. Int. Ed*., 2013, **52**, 12924; (i) H. Liu, G. Jiang, X. Pan, X. Wan, Y. Lai, D. Ma, and W. Xie, *Org. Lett*., 2014, **16**, 1908; (j) Z. Shen, X. Pan, Y. Lai, J. Hu, X. Wan, X. Li, H. Zhang, and W. Xie, *Chem. Sci*., 2015, **6**, 6986.
7. T. Sakai, M. Bito, M. Itakura, H. Sato, and Y. Mori, *Chem. Pharm. Bull*., 2016, **64**, 930.
8. Representative reports for catalytic nucleophilic addition of *N*-acylisoquinolinium or *N*-acylqunolinium satls: (a) M. Takamura, K. Funabashi, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc*., 2000, **122**, 6327; (b) M. S. Taylor, N. Tokunaga, and E. Jacobsen, *Angew. Chem. Int. Ed*., 2005, **44**, 6700; (c) Y. Yamaoka, H. Miyabe, and Y. Takemoto, *J. Am. Chem. Soc*., 2007, **129**, 6686; (d) A. G. Schafer, J. M. Wieting, T. J. Fisher, and A. E. Mattson, *Angew. Chem. Int. Ed*., 2013, **52**, 11321; (e) M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, and O. García Mancheño, *J. Am. Chem. Soc*., 2014, **136**, 13999; (f) S. Shirakawa, S. Liu, S. Kaneko, Y. Kumatabara, A. Fukuda, Y. Omagari, and K. Maruoka, *Angew. Chem. Int. Ed*., 2015, **54**, 15767; (g) M. Zang, W. Sun, G. Zhu, G. Bao, B. Zhang, L. Hong, M. Li, and R. Wang, *ACS Catal*., 2016, **6**, 5290; (h) S. Kaneko, Y. Kumatabara, S. Shimizu, K. Maruoka, and S. Shirakawa, *Chem. Commun*., 2017, **53**, 119; (i) G. Hirata and H. Maeda, *Org. Lett*., 2018, **20**, 2853; (j) S. Benz, A. I. Poblador-Bahamonde, N. Low-Ders, and S. Matile, *Angew. Chem. Int. Ed*., 2018, **57**, 5408; For review: (k) C. Tsukano and Y. Takemoto, 'Asymmetric Dearomatization Reactions: Dearomatization Reactons of Electron-Deficient Aromatic Rings', ed. by S.-L. You, Wiley-VCH, Weinheim, 2016, Chapter 11, pp. 247–

277.

9. (a) R. Yamaguchi, M. Moriyasu, M. Yoshioka, and M. Kawanishi, *J. Org. Chem.*, 1988, **53**, 3507; (b) T. Itoh, M. Miyazaki, K. Nagata, H. Hasegawa, A. Ohsawa, and K. T. Nakamura, *Heterocycles*, 1998, **47**, 125.
10. T. Sakai, J. Matsuoka, M. Shintai, and Y. Mori, *J. Org. Chem.*, 2017, **82**, 3276.