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Enantioselective 1,3-Dipolar Cycloaddition of *C,N*-Cyclic Azomethine Imines to Unsaturated Nitriles Catalyzed by Ni^{II}–Pigiphos

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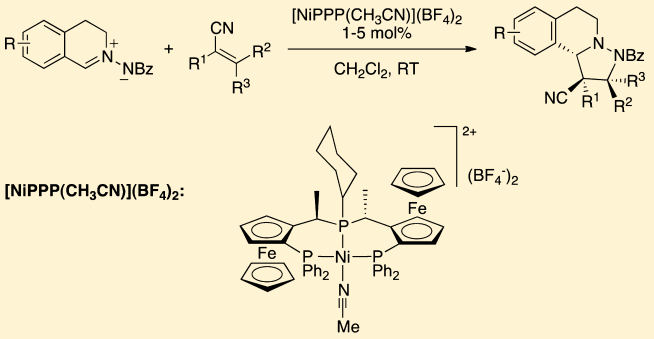
Supporting Information

ABSTRACT: The asymmetric 1,3-dipolar cycloaddition reaction of *C,N*-cyclic azomethine imines with small unsaturated nitriles using a dicationic Ni(II) complex containing the chiral triphosphine ligand bis{(*R*)-1-[(S_p)-2-(diphenylphosphino)-ferrocenyl]ethyl}cyclohexylphosphine [(*R*,S_p)-Pigiphos] as a catalyst has been developed. A variety of new chiral cyanopyrazolidines were obtained regio- and diastereoselectively in good to excellent yields with moderate to excellent enantioselectivities. Thus, *N*-benzoylimino-3,4-dihydro-6-methylisoquinolinium betaine (**1a**) reacts at RT with acrylonitrile in the presence of 1–5 mol % catalyst to afford 3,4-*trans*-1-benzoyl-4-cyano-2,3-(tetrahydroisoquinoline)tetrahydropyrazole (**2a**) in up to 84% yield and 98% *ee*. The regio- and stereoselectivity were confirmed in the case of compound **2a** and 3,4-*trans*-1-benzoyl-4-cyano-2,3-(6-bromotetrahydroisoquinoline)tetrahydropyrazole (**2e**) by X-ray crystallography.



INTRODUCTION

The 1,3-dipolar cycloaddition (1,3-DC) reaction, extensively studied by Huisgen,[1] is certainly a practical route to five-membered heterocycles and generally occurs with high stereocontrol,[2] hence facilitating access to potentially bioactive molecules.[3] Catalytic asymmetric versions are as versatile as they are numerous, ranging from transition-metal-catalyzed to organocatalytic processes. Typical 1,3-dipoles for this class of asymmetric cycloaddition include azomethine ylides, nitrones, and nitronates.[4] However, enantioselective 1,3-DC of alkynes or electron-deficient alkenes with azomethine imines, a less common but yet functionally valuable class of 1,3-dipoles, has recently attracted more attention, thus providing access to enantioenriched pyrazolidines.[5]

Azomethine imines were for a long time limited to acyclic structures, whose generation demands a great activation energy,[6] or to pyrazolidinone-derived *N,N′*-cyclic forms.[7] Novel *C,N*-cyclic *N′*-acyl azomethine imines were then discovered by Tamura[8] and more recently developed by Maruoka and co-workers,[9] thus opening the field to an unexplored class of dipoles. From then on, normal- and inverse-electron-demand asymmetric 1,3-DC with these substrates was realized, first with enals via Ti–binolate catalysis[9] and second with vinyl ethers or acrolein-derived vinylogous azaenamines catalyzed by a chiral dicarboxylic acid.[10] Furthermore, these *C,N*-cyclic azomethine imine substrates were recently used in thermal 1,3-DC with *N*-arylmaleimides,[11] allenoates,[12] and seleno- or thioaldehydes,[13] phosphine-catalyzed [3 + 2] and [4 + 3] annulation reactions with allenoates,[14] and catalyst-free [5 + 1] cycloaddition with isocyanides.[15] Finally, several recent reports concern a variety of metal-catalyzed cycloaddition reactions of azomethine imines,[16] including an enantioselective Ni-catalyzed cycloaddition with alkylidene malonates.[17]

Previous success in our group using dicationic complexes of (R,S_p)-Pigiphos (PPP)[18] with nickel(II)[19] as Lewis acidic catalysts[20−22] led us to test their activity for 1,3-DC with unsaturated nitriles, especially those with low steric demand, for which high selectivity of the cycloadduct is difficult to reach. This category of olefin, activated by its electron-withdrawing group, can also provide a binding site for the coordination of the substrate to the catalyst. When nitrones were chosen as dipoles for the 1,3-DC, the best conversions and selectivities were obtained with $[Ni(PPP)(CH_3CN)](BF_4)_2$.[23] We wished then to investigate various azomethine imines as substrates for the transformation,[6] focusing our attention on *C,N*-cyclic azomethine imines (Scheme 1).

We report herein the first enantioselective 1,3-DC of various *C,N*-cyclic azomethine imines to α,β-unsaturated nitriles. Depending on the size and the mono- or disubstituted nature of the olefin used, these Ni(II)–Pigiphos-catalyzed cycloadditions proceed in a regioselective manner with good diastereoselectivity and moderate to excellent enantioselectivity.

RESULTS AND DISCUSSION

The addition of acrylonitrile to *N*-benzoylimino-3,4-dihydroisoquinolinium betaine (**1a**) performed without catalyst yielded, after 24 h at 60 °C in DCM, four diastereomeric pairs of enantiomers (**2a**, **3a**, **4a**, and **5a**; see Chart 1), but

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Scheme 1. Asymmetric 1,3-DC of Nitrones and *C,N*-Cyclic Azomethine Imines to Acrylonitrile Catalyzed by a Ni(II) Complex with (R,S_p)-Pigiphos (PPP)

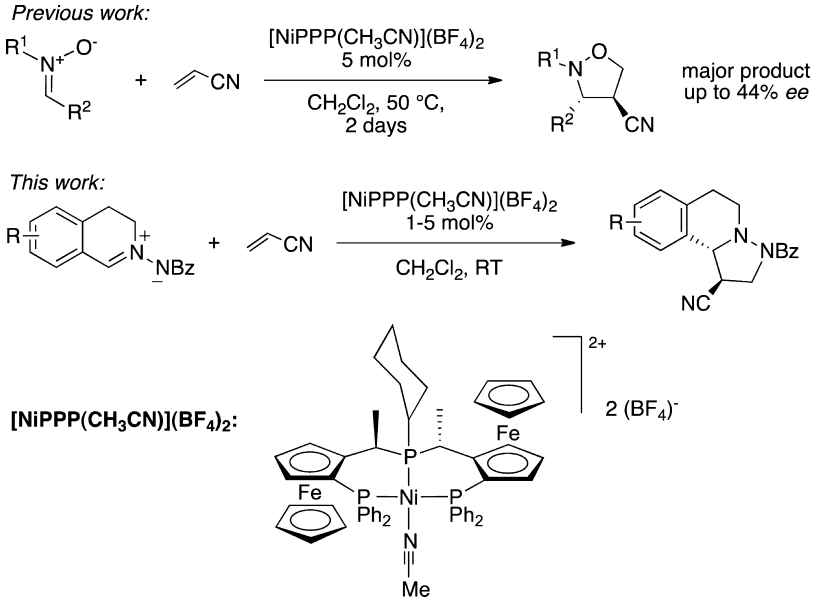
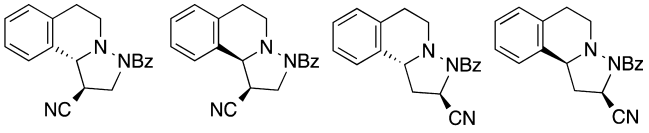


Chart 1. The Four Possible Diastereomeric Forms of the Cycloadducts Derived from Betaine 1a and Acrylonitrile[a]



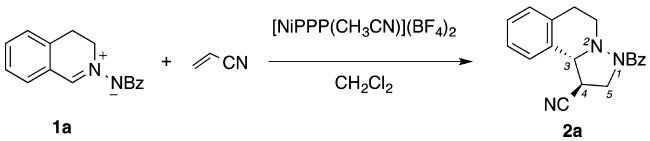
2a **3a** **4a / 5a** **5a / 4a**

[a]**2a** and **3a** are termed 3,4-cycloadducts, and **4a** and **5a** are termed 3,5-cycloadducts. For the latter two isomers, the configuration has not been assigned.

preponderantly the 3,4-cycloadduct regioisomers **2a** and **3a**, as confirmed by 2D NMR experiments. A low diastereomeric excess of 1.1:1 in favor of the 3,4-*trans* isomer **2a** was also observed (Table 1, entry 1). By comparison with bulkier dipolarophiles such as α-substituted allenoates, thermal 1,3-DC of **1a** was reported to yield only the 3,4-cycloadduct with higher *exo* selectivities (from 81:19 to 92:8).[12]

Encouraged by preliminary studies wherein olefinic nitriles were activated by our dicationic Ni(II)−PPP complex, we then catalyzed the above-mentioned reaction using 5 mol % $[Ni(PPP)(CH_3CN)](BF_4)_2$, observing completion of the reaction within only 0.5 and 2.5 h at RT and −78 °C, respectively. Gratifyingly, only the 3,4-regioisomers were formed, with not only good diastereomeric excess of the *trans* isomer **2a** but also excellent enantiomeric excess (entries 2 and 3). We were also able to separate the mixture of *trans* and *cis* diastereomers by column chromatography, accessing **2a** and **3a** as pure pairs of enantiomers. Our system presented such high efficiency at RT in dichloromethane that decreasing the catalyst loading to 1 mol % did not affect the yield or the diastereoselectivity very significantly and resulted in even higher enantioselectivity (entry 4). However, traces of the minor 3,5-regioisomers (**4a** and **5a**) were then detected by ^{1}H NMR spectroscopy (<5% of the major cycloadduct intensity). We also observed a slightly lower rate for the cycloaddition

Table 1. Ni−Pigiphos-Catalyzed 1,3-DC of *C,N*-Cyclic Azomethine Imines: Optimization of the Reaction Conditions



1a **2a**

entry	mol % catalyst	temp	time (h)[a]	yield (%)[b]	*dr* (*trans*/*cis*)[c]	*ee* (%)[d]
1	0	60 °C	24	56[e]	1.1:1 (52:48)	rac.
2	5	RT	0.5	95	11.5:1 (92:8)	96
3	5	−78 °C	2.5	86	6.1:1 (86:14)	94
4	1	RT	1.5	93	5.2:1 (84:16)	98
5[f]	1	RT	3.5	81	5.2:1 (84:16)	93

[a]Complete conversion of the betaine as observed by ^{1}H NMR analysis. [b]Combined yields of the 3,4-cycloadducts (**2a** and **3a**); isolated yields are given in the Experimental Section. [c]Determined by ^{1}H NMR analysis of the crude mixtures; averages of two runs. [d]Determined by chiral HPLC for the major cycloadduct. [e]Combined yield of the 3,4- and 3,5-cycloadducts. [f]Reaction of 0.25 mmol of betaine instead of 0.5 mmol as in the previous entries.

upon reaction scale-down, although a similar yield and selectivity were conserved (entry 5).

The relative stereochemistry of the major product **2a** was established by comparing the ^{1}H NMR shift of the CH(CN) unit with those reported for *trans*- and *cis*-1-acetyl-4-cyano-2-methyl-3-phenyltetrahydropyrazole[24] as well as by an X-ray crystallographic study. Unfortunately, its absolute configuration could not be determined by X-ray crystallographic analysis because this compound preferentially crystallizes as a racemate (as further confirmed by chiral HPLC of the crystalline material). However, anticlockwise optical rotation was observed for our enantioenriched nitrile product **2a**, exactly as for the aldehyde analogue, for which the (3*S*,4*S*) configuration had been previously established.[9] It is therefore reasonable to assume that the preferred enantiomeric form of **2a** as formed in our reaction displays the same absolute configuration. The

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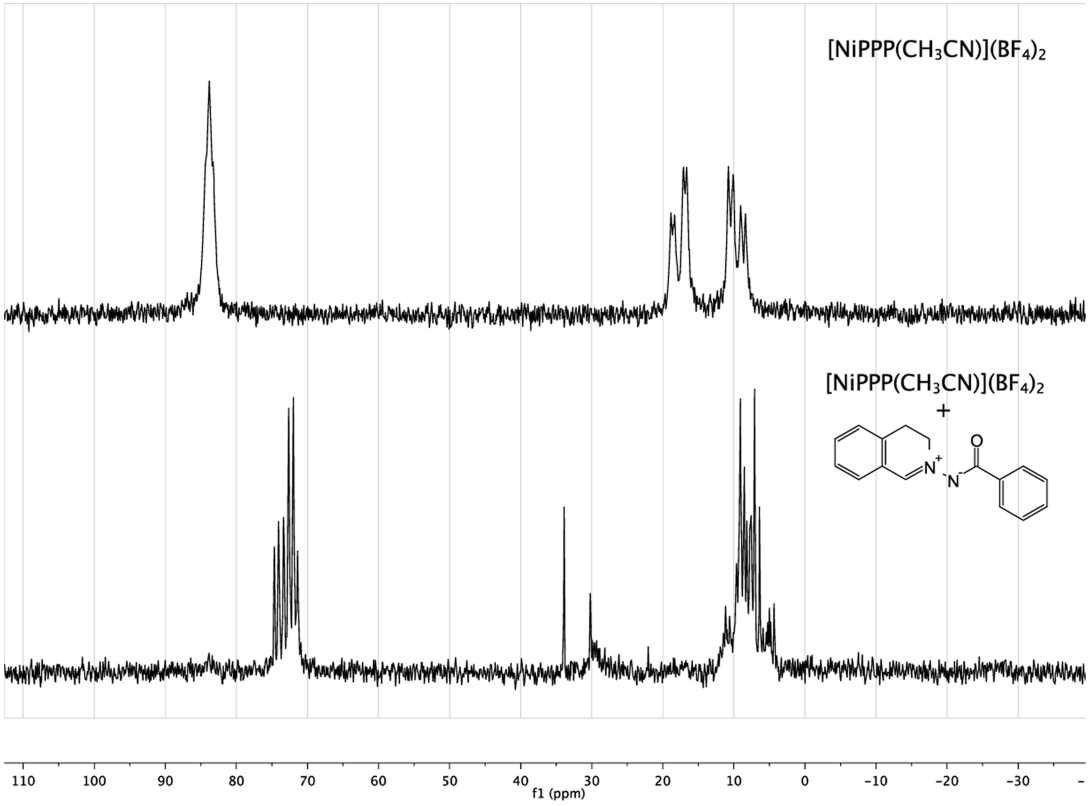

Figure 1. Binding study of $[Ni(PPP)(CH_3CN)](BF_4)_2$ and the azomethine imine substrate **1a** using ^{31}P NMR spectroscopy (121.5 MHz, $CDCl_3$).

molecular structure of **2a** shows a half-chair conformation for the monounsaturated six-membered ring, with the methylene carbon attached to N1 (C6) below and N2 above the ring plane. The fused pyrazolidine has a slightly distorted envelope conformation (C3−C4−C5−N1 torsion angle = −7.3°) with N2 below the ring plane, thereby placing C6 in a pseudoaxial position (see the Supporting Information for ORTEP illustrations and atom numbering).

While unsaturated nitriles unquestionably provide a binding unit for coordination,[21b] the azomethine imine substrate also showed some interaction with the catalyst. Signals in the ^{31}P NMR spectra of $[Ni(PPP)(CH_3CN)](BF_4)_2$ in the presence of 1 equiv of azomethine imine **1a** displayed significant shifts from their initial positions for all three magnetically nonequivalent phosphorus atoms (Figure 1), indicating a different electronic environment for all of them. With an observed ^{31}P NMR high-field shift from +85 to +74 ppm, this was particularly significant for the central cyclohexylphosphine unit, whose phosphorus atom is placed at the position *trans* to the free coordination site of our catalyst. The hereby observed complex formation may arise from coordination via the oxygen atom of the benzoyl protecting group or from the amide nitrogen, although the latter is sterically more hindered. The interaction of **1a** with the catalyst competes with the coordination and activation of the unsaturated nitrile and is likely to be unproductive in view of the catalytic reaction. In fact, the adduct formed by betaine **1a** with the Lewis acidic Ni complex is expected to be significantly less reactive toward the dipolarophile acrylonitrile than is **1a** itself.

The generalization of this asymmetric 1,3-DC of *C,N*-cyclic azomethine imines and acrylonitrile was then investigated. The syntheses of analogous substrates bearing a methyl- (**1b−d**), bromo- (**1e**), or fluoro-substituted (**1f**) fused aromatic ring starting from the corresponding phenethyl alcohols were successful.[25] Unfortunately, for a strong electron-withdrawing group such as CF_3, the corresponding isochroman-type intermediate could not be obtained via the Friedel−Crafts pathway used for other substrates. Under our catalytic conditions, these substrates functionalized with different electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) yielded moderate enantiomeric excesses, from 66% *ee* up to 88% *ee* (Table 2). The *exo* selectivities were good to moderate, gradually decreasing in going from an EDG to an EWG at the position *para* to the 1,3-dipole (entries 1, 6, 8, and 10). The presence of a slightly donating group at the *meta* or *ortho* position affected the *dr* (entries 3 and 5), and a higher enantioselectivity was observed in the latter case (**2d**) than for the *para* and *ortho* analogues. Lower catalyst loading resulted in the same *ee* values but overall longer reaction times and lower *dr* values, especially for the derivative having the methyl group at the position *para* to the dipole, for which the diastereoselectivity dropped from 93:7 with 5 mol % catalyst to 78:22 with 1 mol % (entry 2).

Once again the relative *trans* stereochemistry of the major product could be established in each case by ^1H and 2D NMR spectroscopy, and anticlockwise optical rotation was observed for all of the major cycloadducts **2a−f**. The (3*R*,4*R*) absolute configuration could this time be established by X-ray crystallography of enantiopure crystals of the major diastereomer **2e**, and the enantiopurity was further confirmed by chiral HPLC of the crystalline material. The conformations of the ring systems in the solid state are very similar in **2a** and **2e**, with analogous endocyclic torsion angles. It is also relevant and noteworthy to mention that the (3*R*,5*R*) regioisomer **4e** was synthesized in two steps by Maruoka and co-workers via asymmetric 1,3-DC with *N*-2-propen-1-ylidene-1-pyrrolidin-

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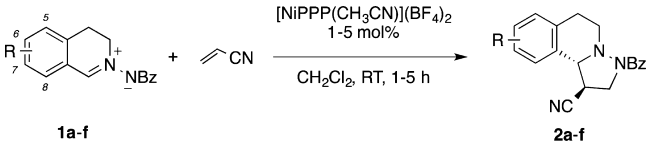
Table 2. Ni−Pigiphos-Catalyzed 1,3-DC of Functionalized *C,N*-Cyclic Azomethine Imines to Acrylonitrile (Bz = Benzoyl)



1a-f 2a-f

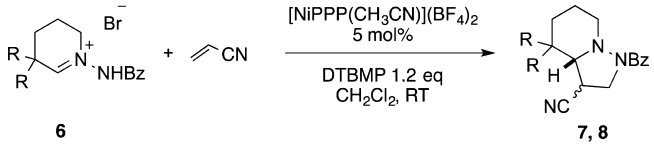
entry	R, **1**	mol % catalyst	time (h)[a]	yield (%)[b]	*dr* (*trans*/*cis*)[c]	*ee* (%)[d]
1	6-Me, **1b**	5	1	95	13.3:1 (93:7)	72
2	6-Me, **1b**	1	5	82	3.5:1 (78:22)	70
3	7-Me, **1c**	5	1	95	7.3:1 (88:12)	72
4	7-Me, **1c**	1	3	83	5.6:1 (85:15)	72
5	8-Me, **1d**	5	1.5	90	6.7:1 (87:13)	88
6	H, **1a**	5	0.5	86	11.5:1 (92:8)	96
7	H, **1a**	1	1.5	93	6.1:1 (86:14)	98
8	6-Br, **1e**	5	1	85	10.1:1 (91:9)	66
9	6-Br, **1e**	1	4	96	4.0:1 (80:20)	64
10	6-F, **1f**	5	0.5	94	5.6:1 (85:15)	74
11	6-F, **1f**	1	1.5	94	4.3:1 (81:19)	74

[a]Complete conversion of the betaine as determined by ^{1}H NMR analysis. [b]Combined yields of the 3,4-cycloadducts; isolated yields are given in the Experimental Section. [c]Determined by ^{1}H NMR analysis of the crude mixtures; a minimum of two reproducible runs. [d]Determined by chiral HPLC for the major cycloadduct.

amine followed by conversion to the nitrile using magnesium monoperoxyphthalate (Scheme 2).[10] However, unlike our compound **2e**, it displayed clockwise optical rotation.

A substrate not having a fused aromatic ring on the *C,N*-cyclic azomethine imine was obtained from hydrobromic salt **6** upon in situ deprotonation by the Brønsted base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Under the above-mentioned catalytic conditions it yielded full conversion within 7 days, but the two *cis*- and *trans*-3,4-cycloadducts (**7** and **8**, respectively) were obtained in equal amounts as racemic mixtures (Scheme 3), most likely suggesting a noncatalyzed transformation. ^{31}P NMR studies showed no interaction between the base and the dicationic Lewis acid catalyst that

Scheme 3. 1,3-DC of Functionalized *C,N*-Cyclic Azomethine Imine 6 with Acrylonitrile[a]



6 **7, 8**

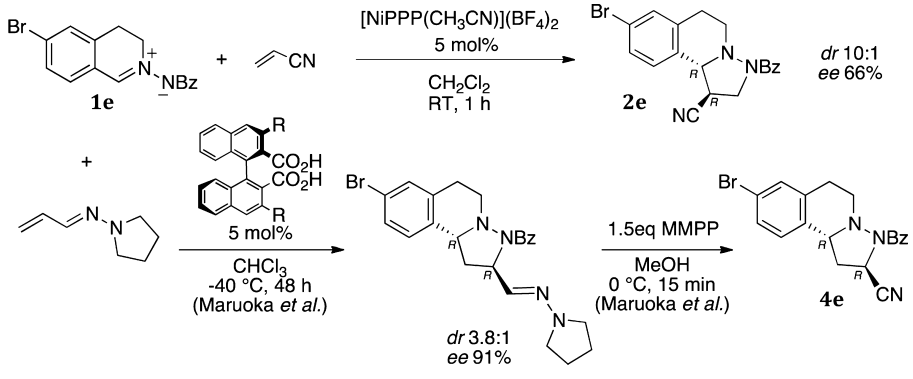
[a]DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, R = −$(CH_2)_5$−, Bz = benzoyl.

could potentially inhibit the catalyst. However, very slow decay of the latter into monocationic [NiCl(PPP)](BF_4) and [NiBr(PPP)](BF_4) was observed in chloroform or methylene chloride over the course of 1 week, the time span for the cycloaddition reaction to proceed.

As a simple dipolarophile such as acrylonitrile was well-tolerated by our system, we investigated the potential influence of a more functionalized cyanoolefin on the *exo* selectivity of the process. Thus, crotononitrile (*trans*/*cis* mixture), methacrylonitrile, *trans*-cinnamonitrile, and *cis*-2-pentenenitrile were reacted with azomethine imine **1a** in dichloromethane in the presence of 5 mol % catalyst at either RT or 40 °C over 48 h. Unfortunately, the reactivities of these disubstituted olefins proved to be much inferior to that of their simpler analogue, as no cycloaddition occurred with *cis*-2-pentenenitrile and *trans*-cinnamonitrile under the same conditions. Also, methacrylonitrile yielded only 52% conversion after 48 h of stirring at 40 °C. The corresponding regio- and diastereoselectivity were also lower, with 37% isolated yield for the 3,4-cycloadducts **2g** and **3g** (*trans*/*cis* = 1.5:1, 41% *ee*/6% *ee*) and 10% isolated yield for the 3,5-cycloadducts **4g** and **5g** (*trans*/*cis* = 1:14). Furthermore, after optimization of the catalyzed reaction conditions (Table 3), addition to betaine **1a** using 4 equiv of crotononitrile (*trans*/*cis* mixture) at RT over 2 days yielded very preponderantly the *trans* 3,4-cycloadduct **2h** (*dr trans*/*cis* 88:12; 66% isolated yield; 62% *ee*) and only traces of the other possible isomers.[26]

For both major cycloadducts **2g** and **2h**, the relative *trans* stereochemistry of the major product could be established by ^{1}H and 2D NMR spectroscopy. Anticlockwise optical rotation as mentioned above for **2a−f** was observed, suggesting a (3*S*,4*R*) configuration for the major enantiomer of **2g** and a (3*R*,4*R*,5*R*) configuration for **2h**. The diastero- and enantiose-

Scheme 2. Two 1,3-Dipolar Cycloadditions of 1e To Access the Enantioenriched (3*R*,4*R*) and (3*R*,5*R*) Regioisomers 2e and 4e, Respectively[a]



[a]R = CH(9,9-Me_2-fluoren-2-yl)$_2$, Bz = benzoyl, MMPP = magnesium monoperoxyphthalate.

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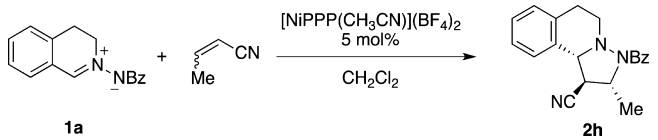
Table 3. Ni−Pigiphos-Catalyzed 1,3-DC of Azomethine Imine 1a with Crotononitrile (*trans*/*cis* Mixture)



1a 2h

entry	mol % catalyst	equiv of olefin	temp	time (days)[a]	yield (%)[b]	*dr* (*trans*/*cis*)[c]	*ee* (%)[d]
1	0	2	40 °C	15	93	1.1:1 (52:48)	rac.
2	5	2	RT	4	96	6.7:1 (87:13)	60
3	5	2	40 °C	2	95	6.7:1 (87:13)	56
4	5	4	RT	2	95	7.3:1 (88:12)	62

[a]Complete conversion of the betaine as observed by ^{1}H NMR analysis. [b]Combined yields of the 3,4-cycloadducts; isolated yields are given in the Experimental Section. [c]Between the two major cycloadducts, as determined by ^{1}H NMR analysis of the crude mixtures. [d]Determined by chiral HPLC for the major cycloadduct; a minimum of two reproducible runs.

lectivities observed with substituted acrylonitrile derivatives were lower than those with acrylonitrile itself but nonetheless significant, indicating that the steric size of the dipolarophile is a crucial factor in these 1,3-DC reactions.

CONCLUSION

In summary, we have successfully developed the asymmetric 1,3-dipolar cycloaddition reaction of *C*,*N*-cyclic azomethine imines with a small activated cyanoolefin such as acrylonitrile, overcoming the fact that high enantioselectivity is usually difficult to reach because of the low steric factor. With our Ni(II)−Pigiphos catalyst, the addition of isochroman-derived azomethine imines with acrylonitrile occurred readily in a regio- and diastereoselective manner with good to excellent enantioselectivity. Our system also catalyzed the 1,3-DC of such azomethine imines with other small α,β-unsaturated nitriles, though with lower enantioselectivities. This work demonstrates the versatility of the dicationic Ni−Pigiphos complex as a Lewis acidic catalyst in asymmetric processes, thereby extending its application scope.

EXPERIMENTAL SECTION

General. All of the reactions were carried out under an argon atmosphere using Schlenk techniques, unless otherwise stated. Anhydrous solvents were freshly distilled under argon from CaH_2 (MeOH, CH_2Cl_2, CH_3CN) or Na/benzophenone (toluene). *N*-Benzoylimino-3,4-dihydroisoquinolinium betaines **1a**−**e** and **6** used as starting materials were synthesized as previously described,[9] and their identities and purities were confirmed by ^{1}H and ^{13}C NMR spectroscopy and HRMS before use. (*R*,*S*$_p$)-Pigiphos[19a] [also denoted as PPP; only the (*R*,*S*$_p$) enantiomer was used throughout] and $[Ni(PPP)(CH_3CN)](BF_4)_2$[19,20c,21a] were prepared from enantiomerically pure (*R*)-Ugi amine[27] following slightly modified literature methods. $[Ni(H_2O)_6][BF_4]_2$, acrylonitrile, methacrylonitrile, crotononitrile (*trans*/*cis* mixture), *trans*-cinnamonitrile, and *cis*-2-pentenenitrile were used as received from commercial suppliers. Chromatographic purification of the products was performed on silica gel 60 (230−400 mesh) under forced flow (ca. 0.1 bar). ^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra were recorded on 200, 250, 300, 400, 500, and 700 MHz spectrometers. Chemical shifts of ^{1}H and ^{13}C signals are reported in parts per million and are calibrated against resonances of the $CDCl_3$ solvent (7.26 and 77.16 ppm, respectively). Coupling constants (*J*) are given in hertz (Hz) as absolute values. Mass spectra were measured on an ESI-QTOF spectrometer. Infrared spectra were measured using an FT ATR spectrometer. Melting point ranges are given without correction. Optical rotations were measured at 589 nm (Na/Hg) at controlled room temperature (20.0 °C) on a polarimeter with an accuracy of ±0.005° using a 10 cm cell and a concentration of 1.0 g/100 mL (*c* 1.0).

Modified Procedure for [Ni(PPP)(MeCN)](BF$_4$)$_2$. (*R*,*S*$_p$)-Pigiphos (885 mg, 0.98 mmol) and $[Ni(H_2O)_6](BF_4)_2$ (333 mg, 0.98 mmol) were mixed in distilled and degassed acetonitrile (25 mL) under Ar to give a brown-purple suspension. The solution was stirred for 8 h at RT and then concentrated, dissolved in dry and degassed DCM, filtered onto Celite under Ar, and dried under high vacuum to afford $[Ni(PPP)(MeCN)](BF_4)_2$ as a purple-black solid (776 mg, 0.66 mmol, 67%). The ^{1}H and ^{31}P NMR data for the cation $[Ni(PPP)(MeCN)]^{2+}$ were identical to those reported for the perchlorate salt $[Ni(PPP)(MeCN)](ClO_4)_2$.

2-(2-Bromoethyl)-4-fluorobenzaldehyde. To a 1 M solution of 6-fluoro-1-methoxyisochroman[25,28] (504 mg, 2.74 mmol) in toluene were added 1 equiv of Bu_4NBr (884 mg, 2.74 mmol) and 2 equiv of TMSBr (720 μL, 5.49 mmol) at RT. The reaction flask was sealed and then warmed to 80 °C and stirred for 4 h. The mixture was poured into saturated aq. $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel eluting with hexane/DCM to give the aldehyde as a colorless oil (500 mg, 2.16 mmol, 79%) that decomposes when exposed to air. ^{1}H NMR (250 MHz, $CDCl_3$): δ 10.10 (s, 1H), 7.85 (dd, *J* = 8.5, 5.8 Hz, 1H), 7.16 (td, *J* = 8.2, 2.5 Hz, 1H), 7.06 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.70−3.50 (m, 4H). Full characterization was performed after derivatization to give azomethine imine **1f**.

***N*-Benzoylimino-3,4-dihydro-6-fluoroisoquinolinium betaine (1f).** To a 0.5 M solution of 2-(2-bromoethyl)-4-fluorobenzaldehyde (450 mg, 1.96 mmol) in MeOH was added benzoylhydrazine (250 mg, 1.83 mmol) at RT. After the immediate formation of an insoluble material, the white suspension was heated to reflux and stirred for an additional hour to give a clear solution. The reaction solution was cooled to RT, treated with Et_3N (0.38 mL, 2.75 mmol), poured into water, and stirred for 30 min to give a white-yellow precipitate. The solid material was washed with cold ether and then dissolved in CH_2Cl_2 to give a yellow solution, which was dried over Na_2SO_4 and evaporated to give *N*-benzoylimino-3,4-dihydro-6-fluoroisoquinolium betaine (**1f**) as a yellow solid (300 mg, 1.12 mmol, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.09 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.55−7.33 (m, 4H), 7.08 (td, *J* = 8.4, 2.4 Hz, 1H), 7.02 (dd, *J* = 8.5, 2.4 Hz, 1H), 4.25 (t, *J* = 7.6 Hz, 2H), 3.25 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.8, 165.4 (d, *J* = 257.0 Hz), 146.0, 137.2, 136.9 (d, *J* = 9.0 Hz), 132.0 (d, *J* = 9.5 Hz), 130.5, 128.1, 128.0, 123.6 (d, *J* = 3.0 Hz), 115.6 (d, *J* = 22.5 Hz), 115.6 (d, *J* = 22.8 Hz), 54.3, 27.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ −103.4. IR (neat) 3056, 2920, 2852, 1647 (C═O), 1616, 1592, 1577, 1534, 1489, 1288, 1267, 1244, 1143, 1072 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{16}H_{14}FN_2O$, 269.1085 ([M + H]$^+$); found, 269.1081 ([M + H]$^+$).

General Procedure for Uncatalyzed Reactions of *C*,*N*-Cyclic Azomethine Imines and Acrylonitrile. In a dry Young−Schlenk flask, **1a** (251 mg, 1.0 mmol) was dissolved in dry dichloromethane (14 mL), and acrylonitrile (0.13 mL, 2.0 mmol) was added. The reaction mixture was then heated to 60 °C for 24 h. Solvent and excess acrylonitrile were evaporated to give a slightly beige solid. Diastereomeric excess was then determined for the major regioisomer

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by ^{1}H NMR analysis of the crude mixture after filtration on a silica plug eluting with hexane/ethyl acetate 1:1 (*dr* 3,4-*trans*/*cis* = 52:48). The latter was purified by column chromatography (hexane/ethyl acetate 4:1) to give the four cycloadducts in the following order of elution: major 3,5-cycloadduct **4a** (10 mg, 0.03 mmol), minor 3,5-cycloadduct **5a** (9 mg, 0.03 mmol; mixture 1:1 with **4a**), 3,4-*trans*-cycloadduct **2a** (79 mg, 0.26 mmol), 3,4-*cis*-cycloadduct **3a** (71 mg, 0.23 mmol). Overall cycloaddition yield: 169 mg, 0.56 mmol, 56%.

General Procedure for Ni(PPP)-Catalyzed Reactions of *C,N*-Cyclic Azomethine Imines and Acrylonitrile. $[Ni(PPP)(CH_3CN)](BF_4)_2$ (1−5 mol %) and acrylonitrile (2 equiv) were successively added to a solution of betaine **1** (1 equiv) in freshly distilled dichloromethane (7.0 mL per 0.5 mmol of **1**) in a dry Young−Schlenk flask under an Ar atmosphere. The solution was stirred for 0.5−5 h at RT and then concentrated to remove the excess acrylonitrile. The diastereomeric excess was determined by ^{1}H NMR analysis of the crude mixture after filtration on a silica plug eluting with hexane/ethyl acetate 1:1. The residue was purified by column chromatography on silica gel (eluting with hexane/ethyl acetate 4:1) to give the 3,4-*trans*- and 3,4-*cis*-cycloadducts (**2** and **3**, respectively). The enantiomeric purity of the major 3,4-*trans*-cycloadduct **2** was determined by chiral HPLC.

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-2,3-(tetrahydroisoquinoline)tetrahydropyrazole (2a and 3a, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-6-methylisoquinolinium betaine **1a** (125 mg, 0.5 mmol) and 5 mol % catalyst, stirring for 0.5 h. The crude yield and diastereomeric excess were measured (145 mg, 0.48 mmol, 95%; *dr trans*/*cis* = 92:8), and column chromatography gave the 3,4-*trans*- and 3,4-*cis*-cycloadducts **2a** (128 mg, 0.42 mmol, 84%; 96% *ee*) and **3a** (9 mg, 0.03 mmol, 6%), respectively, as white solids. The enantiomeric purity of **2a** was determined by chiral HPLC. 3,4-*trans* cycloadduct (major) **2a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, J = 7.0 Hz, 2H), 7.55−7.50 (m, 1H), 7.48−7.43 (m, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.32−7.25 (m, 2H), 7.17−7.12 (m, 1H), 4.60 (d, J = 9.8 Hz, 1H), 4.51 (dd, J = 12.2, 7.8 Hz, 1H), 4.14 (dd, J = 12.2, 10.3 Hz, 1H), 3.41 (pseudo-td, J = 10.0, 7.8 Hz, 1H), 3.10−2.97 (m, 2H), 2.87−2.78 (m, 1H), 2.77−2.70 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 134.1, 132.5, 131.8, 131.1, 128.8, 128.7, 128.5, 128.0, 127.2, 127.0, 119.3, 66.3, 48.2, 47.9, 35.4, 29.0. IR (neat): 3061, 2939, 2897, 2850, 2243 (C≡N), 1632 (C═O), 1574, 1496, 1448, 1417, 1351, 1279, 1228, 1178, 1127, 1066, 1029, 1003, 935 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{18}N_3O$, 304.1444 ([M + H]$^+$); found, 304.1440 ([M + H]$^+$). $[\alpha]_D^{20}$ −38.4 (*c* 1.0, $CHCl_3$; 96% *ee*). Mp 75−76 °C. Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 65 min (major), 105 min (minor). X-ray-quality crystals were obtained by recrystallization in MeOH/diethyl ether. 3,4-*cis* cycloadduct (minor) **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 7.0 Hz, 2H), 7.51−7.40 (m, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.32−7.27 (m, 1H), 7.25−7.15 (m, 1H), 7.16−7.11 (m, 1H), 4.75 (dd, J = 12.6, 9.9 Hz, 1H), 4.61 (d, J = 8.0 Hz, 1H), 4.10 (dd, J = 12.6, 4.3 Hz, 1H), 3.82 (ddd, J = 9.9, 8.0, 4.3 Hz, 1H), 3.51−3.29 (m, 1H), 3.19−3.09 (m, 1H), 3.07−2.95 (m, 1H), 2.93−2.77 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 134.2, 133.7, 131.1, 130.6, 129.0, 128.7, 128.5, 128.0, 127.3, 127.1, 119.8, 64.8, 48.1, 47.9, 35.8, 29.1. IR (neat): 2925, 2854, 2240 (C≡N), 1627 (C═O), 1574, 1494, 1447, 1417, 1351, 1275, 1228, 1179, 1115, 1063, 1027, 1003, 938 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{18}N_3O$, 304.1444 ([M + H]$^+$); found, 304.1449 ([M + H]$^+$). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 65 min, 77 min.

3,5-*trans*- and 3,5-*cis*-1-Benzoyl-5-cyano-2,3-(tetrahydroisoquinoline)tetrahydropyrazole (4a and 5a). Prepared according to the uncatalyzed procedure. 3,5-cycloadduct (major) **4a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 7.25−7.18 (m, 2H), 7.18−7.12 (m, 1H), 7.11−7.04 (m, 1H), 5.27 (dd, J = 9.5, 8.0 Hz, 1H), 4.39 (dd, J = 11.0, 7.0 Hz, 1H), 3.33−3.22 (m, 2H), 3.14−2.99 (m, 2H), 2.82−2.74 (m, 1H), 2.75−2.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 133.6, 133.4, 132.6, 131.5, 129.1, 128.9, 128.0, 127.7, 126.9, 126.8, 119.3, 62.8, 48.4, 45.5, 38.5, 29.5. IR (neat): 2950, 2845, 2239 (C≡N), 1650 (C═O), 1598, 1579, 1493, 1448, 1425, 1374, 1343, 1304, 1261, 1177, 1112, 1064, 1034, 1022, 1002, 928 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{18}N_3O$, 304.1444 ([M + H]$^+$); found, 304.1445 ([M + H]$^+$). 3,5-cycloadduct (minor) **5a**: ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.12 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.29−7.22 (m, 3H), 7.20 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 5.06 (dd, J = 9.5, 1.5 Hz, 1H), 4.88 (dd, J = 12.0, 5.8 Hz, 1H), 2.95 (ddd, J = 16.5, 13.0, 4.8 Hz, 1H), 2.88 (ddd, J = 13.0, 5.8, 1.5 Hz, 1H), 2.84−2.80 (m, 1H), 2.68−2.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 133.6, 133.3, 132.6, 131.5, 129.1, 128.9, 128.0, 127.7, 126.9, 126.8, 119.3, 62.8, 48.4, 45.5, 38.5, 29.4. IR (neat): 2921, 2851, 2242 (C≡N), 1632 (C═O), 1574, 1492, 1448, 1402, 1343, 1316, 1279, 1249, 1178, 1112, 1066, 1027, 973, 907 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{18}N_3O$, 304.1444 ([M + H]$^+$); found, 304.1447 ([M + H]$^+$).

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-2,3-(6-methyltetrahydroisoquinoline)tetrahydropyrazole (2b and 3b, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-6-methylisoquinolinium betaine **1b** (45 mg, 0.17 mmol) and 5 mol % catalyst, stirring for 1 h. The crude yield and diastereomeric excess were measured (51 mg, 0.16 mmol, 95%; *dr trans*/*cis* = 93:7), and column chromatography gave the 3,4-*trans*- and 3,4-*cis*-cycloadducts **2b** (30 mg, 0.094 mmol, 55%; 72% *ee*) and **3b** (3 mg, 0.008 mmol, 5%), respectively, as white solids. 3,4-*trans* cycloadduct (major) **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.2 Hz, 2H), 7.50−7.42 (m, 1H), 7.42−7.33 (m, 3H), 7.09 (d, J = 7.9 Hz, 1H), 6.96 (s, 1H), 4.57 (d, J = 9.7 Hz, 1H), 4.46 (dd, J = 12.0, 8.0 Hz, 1H), 4.13 (dd, J = 12.0, 10.3 Hz, 1H), 3.37 (pseudo-td, J = 10.0, 8.0 Hz, 1H), 3.10−2.91 (m, 2H), 2.87−2.74 (m, 1H), 2.73−2.63 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 138.4, 134.1, 132.3, 131.1, 129.3, 128.9, 128.7, 128.0, 127.9, 126.8, 119.4, 66.2, 48.3, 47.9, 35.5, 29.0, 21.2. IR (neat): 2961, 2242 (C≡N), 1629 (C═O), 1573, 1494, 1447, 1412, 1280, 1260, 1178, 1092, 1016, 940 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1598 ([M + H]$^+$). $[\alpha]_D^{20}$ −35.0 (*c* 1.0, $CHCl_3$; 72% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 48 min (major), 74 min (minor). 3,4-*cis* cycloadduct (minor) **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 7.00 (s, 1H), 4.73 (pseudo-t, J = 11.5 Hz, 1H), 4.58 (d, J = 8.0 Hz, 1H), 4.10 (dd, J = 12.5, 4.2 Hz, 1H), 3.79 (ddd, J = 10.0, 8.0, 4.2 Hz, 1H), 3.41−3.30 (m, 1H), 3.14−3.06 (m, 1H), 3.06−2.93 (m, 1H), 2.83−2.72 (m, 1H), 2.32 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.0, 138.2, 134.2, 133.5, 131.1, 129.6, 128.8, 128.0, 127.9, 127.5, 127.1, 119.9, 64.7, 48.2, 47.9, 35.8, 29.0, 21.3. IR (neat): 2961, 2954, 2238 (C≡N), 1627 (C═O), 1574, 1448, 1414, 1259, 1089, 1016, 966, 912 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1601 ([M + H]$^+$).

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-2,3-(7-methyltetrahydroisoquinoline)tetrahydropyrazole (2c and 3c, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-7-methylisoquinolinium betaine **1c** (83 mg, 0.31 mmol) and 1 mol % catalyst, stirring for 3 h. The crude yield and diastereomeric excess were measured (81 mg, 83%; *dr trans*/*cis* = 85:15), and column chromatography gave the 3,4-*trans*- and 3,4-*cis*-cycloadducts **2c** (76 mg, 0.24 mmol, 77%; 72% *ee*) and **3c** (4 mg, 0.013 mmol, 4%), respectively, as white solids. 3,4-*trans* cycloadduct (major) **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 4.55 (d, J = 10.0 Hz, 1H), 4.48 (dd, J = 12.0, 7.8 Hz, 1H), 4.13 (dd, J = 12.0, 10.0 Hz, 1H), 3.39 (pseudo-td, J = 10.0, 7.8 Hz, 1H), 3.08−2.90 (m, 2H), 2.80 (ddd, J = 12.0, 10.0, 3.0 Hz, 1H), 2.73−2.64 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 137.0, 134.1, 131.7, 131.1, 129.4, 129.4, 128.8, 128.7, 128.0, 127.3, 119.4, 66.4, 48.4, 47.9, 35.4, 28.7, 21.2. IR (neat): 2928, 2242 (C≡N), 1624 (C═O), 1574, 1506, 1448, 1416, 1350, 1278, 1235, 1119, 1027, 933 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1606 ([M + H]$^+$). $[\alpha]_D^{20}$ −40.9 (*c* 1.0, $CHCl_3$; 72% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 46 min

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(major), 64 min (minor). 3,4-*cis* cycloadduct (minor) **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.1 Hz, 2H), 7.49−7.40 (m, 1H), 7.37 (t, J = 7.4 Hz, 2H), 7.10−7.05 (m, 2H), 6.92 (s, 1H), 4.73 (dd, J = 12.5, 10.0 Hz, 1H), 4.55 (d, J = 8.0 Hz, 1H), 4.10 (dd, J = 12.5, 4.2 Hz, 1H), 3.79 (ddd, J = 10.0, 8.0, 4.2 Hz, 1H), 3.36 (ddd, J = 12.5, 10.5, 3.4 Hz, 1H), 3.10 (ddd, J = 10.5, 5.0, 1.4 Hz, 1H), 2.98 (ddd, J = 16.5, 12.5, 5.0 Hz, 1H), 2.78 (pseudo-dt, J = 16.5, 2.4 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 136.7, 134.2, 131.1, 130.6, 130.4, 129.4, 128.8, 128.7, 127.9, 127.6, 119.9, 64.8, 48.2, 48.0, 35.8, 28.6, 21.2. IR (neat): 2922, 2851, 2241 (C≡N), 1630 (C═O), 1574, 1506, 1448, 1423, 1288, 1220, 1113, 1029, 973, 934 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1598 ([M + H]$^+$).

3,4-*trans*-1-Benzoyl-4-cyano-2,3-(8-methyltetrahydroisoquinoline)tetrahydropyrazole (2d). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-8-methylisoquinolinium betaine **1d** (26 mg, 0.10 mmol) and 5 mol % catalyst, stirring for 1.5 h. The crude yield and diastereomeric excess were measured (29 mg, 0.09 mmol, 90%; *dr trans/cis* = 87:13), and column chromatography gave the 3,4-*trans*-cycloadduct **2d** (15 mg, 0.047 mmol, 47%; 88% *ee*) as a clear oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.85 (d, J = 7.5 Hz, 2H), 7.46 (tt, J = 7.0, 1.3 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 4.77 (d, J = 9.3 Hz, 1H), 4.69−4.57 (m, 1H), 4.14 (pseudo-t, J = 11.1 Hz, 1H), 3.36 (pseudo-dt, J = 9.7, 6.8 Hz, 1H), 3.12−3.07 (m, 1H), 3.03−2.96 (m, 2H), 2.83 (dd, J = 12.4, 2.0 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 136.9, 133.9, 133.0, 131.2, 130.1, 129.6, 128.9, 128.2, 128.0, 126.6, 119.9, 64.8, 48.5, 48.0, 34.8, 29.1, 20.8. IR (neat): 2927, 2241 (C≡N), 1631 (C═O), 1575, 1466, 1448, 1417, 1350, 1269, 1229, 1179, 1070, 1027, 971, 939 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{20}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1599 ([M + H]$^+$). $[\alpha]_D^{20}$ −24.4 (c 1.0, $CHCl_3$; 88% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 50 min (major), 72 min (minor).

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-2,3-(6-bromotetrahydroisoquinoline)tetrahydropyrazole (2e and 3e, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-6-bromoisoquinolinium betaine **1e** (46 mg, 0.141 mmol) and 5 mol % catalyst, stirring for 1 h. The crude yield and diastereomeric excess were measured (46 mg, 0.120 mmol, 85%; *dr trans/cis* = 91:9), and column chromatography gave the 3,4-*trans*- and 3,4-*cis*-cycloadducts **2e** (41 mg, 0.107 mmol, 76%; 66% *ee*) and **3e** (4 mg, 0.010 mmol, 7%), respectively, as white solids. 3,4-*trans* cycloadduct (major) **2e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.4 Hz, 2H), 7.50−7.35 (m, 5H), 7.34−7.30 (m, 1H), 4.54 (d, J = 9.8 Hz, 1H), 4.48 (dd, J = 12.0, 8.0 Hz, 1H), 4.13 (dd, J = 12.0, 10.3 Hz, 1H), 3.37 (pseudo-td, J = 10.0, 8.0 Hz, 1H), 3.12−2.94 (m, 2H), 2.85−2.66 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 134.8, 134.0, 131.8, 131.2, 130.8, 130.4, 128.7, 128.5, 128.1, 122.5, 119.0, 66.0, 47.9, 47.9, 35.3, 28.9. IR (neat): 2923, 2239 (C≡N), 1631 (C═O), 1598, 1574, 1485, 1448, 1419, 1350, 1274, 1229, 1187, 1123, 1077, 1003, 935 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{17}BrN_3O$, 382.0550, 384.0530 ([M + H]$^+$; ^{79}Br, ^{81}Br); found, 382.0546, 384.0529 ([M + H]$^+$; ^{79}Br, ^{81}Br). $[\alpha]_D^{20}$ −29.2 (c 1.0, $CHCl_3$; 66% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 80 min (major), 110 min (minor). Mp: 149−152 °C. X-ray-quality crystals of the major enantiomer were obtained by recrystallization in MeOH. 3,4-*cis* cycloadduct (minor) **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.2 Hz, 2H), 7.49−7.34 (m, 5H), 7.00 (d, J = 8.2 Hz, 1H), 4.75 (pseudo-t, J = 11.2 Hz, 1H), 4.54 (d, J = 8.0 Hz, 1H), 4.08 (dd, J = 12.6, 4.2 Hz, 1H), 3.80 (ddd, J = 10.0, 8.0, 4.2 Hz, 1H), 3.40−3.28 (m, 1H), 3.13 (dd, J = 10.6, 5.1 Hz, 1H), 3.08−2.95 (m, 1H), 2.81 (dt, J = 16.5, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 136.0, 134.1, 132.0, 131.2, 130.3, 129.6, 128.8, 128.7, 128.0, 122.4, 119.5, 64.4, 48.1, 47.5, 35.6, 28.9. IR (neat): 2923, 2239 (C≡N), 1629 (C═O), 1598, 1574, 1485, 1447, 1417, 1271, 1228, 1117, 1074, 1005, 967, 910 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{17}BrN_3O$, 382.0550, 384.0530 ([M + H]$^+$; ^{79}Br, ^{81}Br); found, 382.0552, 384.0534 ([M + H]$^+$; ^{79}Br, ^{81}Br).

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-2,3-(6-fluorotetrahydroisoquinoline)tetrahydropyrazole (2f and 3f, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydro-6-fluoroisoquinolinium betaine **1f** (28 mg, 0.105 mmol) and 5 mol % catalyst, stirring for 0.5 h. The crude yield and diastereomeric excess were measured (31.5 mg, 94%; *dr trans/cis* = 85:15), and column chromatography gave the 3,4-*trans*- and 3,4-*cis*-cycloadducts **2f** (26 mg, 0.081 mmol, 77%; 74% *ee*) and **3f** (4.5 mg, 0.014 mmol, 13%), respectively, as white solids. 3,4-*trans* cycloadduct (major) **2f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.80 (m, 2H), 7.53−7.44 (m, 2H), 7.42−7.34 (m, 2H), 7.00 (td, J = 8.4, 2.5 Hz, 1H), 6.85 (dd, J = 9.1, 2.4 Hz, 1H), 4.56 (d, J = 9.7 Hz, 1H), 4.48 (dd, J = 12.2, 8.0 Hz, 1H), 4.14 (dd, J = 12.2, 10.3 Hz, 1H), 3.38 (pseudo-td, J = 10.1, 8.0 Hz, 1H), 3.11−2.94 (m, 2H), 2.86−2.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 162.5 (d, J = 248.4 Hz), 135.0 (d, J = 7.6 Hz), 134.0, 131.2, 128.7, 128.7 (d, J = 8.7 Hz), 128.0, 127.6 (d, J = 2.9 Hz), 119.1, 115.4 (d, J = 21.4 Hz), 114.6 (d, J = 22.0 Hz), 66.0, 47.8, 47.8, 35.5, 29.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −113.0. IR (neat): 2930, 2242 (C≡N), 1616 (C═O), 1591, 1573, 1500, 1448, 1419, 1274, 1246, 1145, 1012, 923 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{17}FN_3O$, 322.1350 ([M + H]$^+$); found, 322.1345 ([M + H]$^+$). $[\alpha]_D^{20}$ −33.3 (c 1.0, $CHCl_3$; 74% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 64 min (major), 97 min (minor). 3,4-*cis* cycloadduct (minor) **3f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dt, J = 7.1, 1.4 Hz, 2H), 7.46 (t, J = 6.8 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 7.11 (dd, J = 8.6, 5.4 Hz, 1H), 7.00 (td, J = 8.3, 2.3 Hz, 1H), 6.91 (dd, J = 9.3, 2.5 Hz, 1H), 4.76 (dd, J = 12.5, 10.0 Hz, 1H), 4.57 (d, J = 8.0 Hz, 1H), 4.09 (dd, J = 12.5, 4.3 Hz, 1H), 3.79 (ddd, J = 10.0, 8.0, 4.3 Hz, 1H), 3.36 (ddd, J = 12.0, 10.6, 3.5 Hz, 1H), 3.13 (ddd, J = 10.6, 5.2, 1.8 Hz, 1H), 3.03 (ddd, J = 16.7, 12.0, 5.2 Hz, 1H), 2.82 (pseudo-dt, J = 16.7, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 162.33 (d, J = 248.1 Hz), 136.2 (d, J = 8.0 Hz), 134.1, 131.2, 129.0 (d, J = 8.7 Hz), 128.7, 128.0, 126.4 (d, J = 2.8 Hz), 119.6, 115.6 (d, J = 21.4 Hz), 114.7 (d, J = 22.2 Hz), 64.4, 48.1, 47.4, 35.8, 29.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ −113.0. IR (neat) 2949, 2241 (C≡N), 1617 (C═O), 1591, 1574, 1501, 1448, 1415, 1273, 1248, 1221, 1145, 1106, 1012, 969, 927 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{19}H_{17}FN_3O$, 322.1350 ([M + H]$^+$); found, 322.1356 ([M + H]$^+$).

(3′*R,3a′*S**)- and (3′*R**,3a′*R**)-1′-Benzoylhexahydro-1′*H*-spiro[cyclohexane-1,4′-pyrazolo[1,5-*a*]pyridine]-3′-carbonitrile (7 and 8, Respectively).** Prepared according to the general procedure with *N*-benzoylimino-2,3,4,5-tetrahydropyridinium bromide **6** (107 mg, 0.305 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (75 mg, 0.366 mmol, 1.2 equiv) at RT, stirring for 7 days. The crude yield and diastereomeric excess were measured (96% yield; *dr* 3,4-*trans*/*cis* = 1:1), and column chromatography gave, in order of elution, the 3,4-*cis* cycloadduct **7** (48 mg, 0.148 mmol, 49%; racemic) and 3,4-*trans* cycloadduct **8** (22 mg, 0.068 mmol, 22%; racemic) as white solids. 3,4-*cis* cycloadduct **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 7.3 Hz, 1H), 7.36 (t, J = 7.4 Hz, 2H), 4.49 (dd, J = 12.8, 9.8 Hz, 1H), 4.04 (dd, J = 12.8, 3.4 Hz, 1H), 3.29 (ddd, J = 9.8, 7.0, 3.4 Hz, 1H), 3.17 (d, J = 7.0 Hz, 1H), 2.95 (ddd, J = 13.2, 10.8, 3.1 Hz, 1H), 2.80 (d, J = 10.6 Hz, 1H), 2.07−1.17 (m, 14H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.3, 134.5, 130.8, 128.6, 127.8, 122.4, 70.8, 50.0, 49.0, 36.2, 36.2, 35.5, 28.0, 27.4, 26.1, 21.6, 21.3, 21.2, 19.9. IR (neat): 2927, 2855, 2235 (C≡N), 1624 (C═O), 1590, 1573, 1518, 1448, 1269, 1218, 1176, 1105, 1068, 1026, 999, 933, 911 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{20}H_{26}N_3O$, 324.2070 ([M + H]$^+$); found, 324.2066 ([M + H]$^+$). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 47 min, 71 min. 3,4-*trans* cycloadduct **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.38 (t, J = 7.4 Hz, 2H), 4.45−4.35 (m, 1H), 4.08 (dd, J = 12.5, 9.8 Hz, 1H), 3.37 (d, J = 10.6 Hz, 1H), 3.40−3.26 (m, 1H), 2.79 (d, J = 10.8 Hz, 1H), 2.33 (dd, J = 11.8, 2.5 Hz, 1H), 1.83−1.02 (m, 14H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 134.2, 130.9, 128.7, 127.9, 120.2, 73.9, 50.1, 47.7, 37.0, 35.7, 35.0, 27.3, 26.8, 26.2, 21.4, 21.3, 19.6. IR (neat): 2924, 2852, 2240 (C≡N), 1625 (C═O), 1590, 1573, 1448, 1424, 1284, 1232, 1200, 1178, 1115, 1071, 1027, 940, 907 cm^{-1}. HRMS (ESI) m/z: calcd for

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$C_{20}H_{26}N_3O$, 324.2070 ([M + H]$^+$); found, 324.2068 ([M + H]$^+$). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 32 min, 38 min.

3,4-*trans*- and 3,4-*cis*-1-Benzoyl-4-cyano-4-methyl-2,3-(tetrahydroisoquinoline)tetrahydropyrazole (2g and 3g, Respectively). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydroisoquinolinium betaine **1a** (47 mg, 0.188 mmol) and methacrylonitrile (32 μL, 0.38 mmol) at 40 °C, stirring for 2 days. The conversion and diastereomeric excess were determined by ^{1}H NMR analysis (52% conversion, regioselectivity 3,4/3,5-cycloadducts = 3:1; *dr* 3,4-*trans*/*cis* = 1.5:1, *dr* 3,5-*trans*/*cis* = 1:15), and column chromatography gave the 3,4-*trans* and 3,4-*cis* cycloadducts **2g** and **3g** (22 mg, 0.069 mmol, 37%; *trans*/*cis* = 1.5:1, 41% *ee*/6% *ee*) as a white solid as well as the 3,5-*trans* and 3,5-*cis* cycloadducts **4g** and **5g** (6 mg, 0.019 mmol, 10%; *trans*/*cis* = 1:14). 3,4-*trans* and *cis* cycloadducts **2g** and **3g** (ratio 1.5:1): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (t, *J* = 7.1 Hz, 5H), 7.47 (t, *J* = 7.3 Hz, 2.5H), 7.46−7.37 (m, 7.5H), 7.35−7.27 (m, 5H), 7.23 (dd, *J* = 6.9, 2.2 Hz, 1.5H), 7.18 (d, *J* = 6.5 Hz, 1H), 5.04 (d, *J* = 12.0 Hz, 1.5H), 4.88 (s, 1.5H), 4.46−4.33 (m, 2H), 4.21 (s, 1H), 3.77 (d, *J* = 12.7 Hz, 1.5H), 3.60−3.48 (m, 1H), 3.23−2.94 (m, 6.5H), 2.89 (dd, *J* = 15.3, 2.4 Hz, 1H), 2.78 (d, *J* = 16.4 Hz, 1.5H), 1.89 (s, 3H), 1.36 (s, 4.5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 134.0, 133.7, 131.1, 130.6, 129.8, 129.2, 129.1, 128.8, 128.4, 128.0, 127.9, 127.4, 127.0, 126.8, 126.4, 124.2, 72.0, 69.9, 64.6, 55.6, 49.6, 47.8, 43.1, 29.8, 28.8, 25.6, 24.6. IR (neat): 2924, 2852, 2234 (C≡N), 1630 (C═O), 1590, 1574, 1494, 1447, 1412, 1382, 1280, 1248, 1213, 1180, 1120, 1060, 1028, 915 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{19}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1605 ([M + H]$^+$). $[\alpha]_D^{20}$ −17.8 (*c* 1.0, $CHCl_3$; *trans*/ *cis* = 1.5:1, 41% *ee*/6% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.5 mL/min) retention time: 36 min (*trans* major), 50 min (*cis* minor), 52 min (*trans* minor), 92 min (*cis* major). 3,5-*trans* and *cis* cycloadducts **4g** and **5g** (ratio 1:14): the ^{1}H and COSY NMR and HRMS (ESI) data for **4g** and **5g** coincided with those reported in the literature.[10]

3,4-*trans*-1-Benzoyl-4-cyano-5-methyl-2,3-(tetrahydroisoquinoline)tetrahydropyrazole (2h). Prepared according to the general procedure with *N*-benzoylimino-3,4-dihydroisoquinolinium betaine **1a** (53 mg, 0.212 mmol), crotononitrile (*trans*/*cis* mixture, 69 μL, 0.847 mmol, 4 equiv), and 5 mol % catalyst, stirring at RT for 2 days. The conversion and diastereomeric excess were measured (95% conversion; *dr* 3,4-*trans*/*cis* = 88:12), and column chromatography gave the 3,4-*trans*-cycloadduct **2h** (44 mg, 0.139 mmol, 66%; 62% *ee*) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82−7.75 (m, 2H), 7.51 (dd, *J* = 5.5, 3.5 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.27 (dd, *J* = 5.5, 3.5 Hz, 2H), 7.14 (dd, *J* = 5.5, 3.5 Hz, 1H), 4.88 (dq, *J* = 8.7, 6.5 Hz, 1H), 4.52 (d, *J* = 10.4 Hz, 1H), 3.24 (dd, *J* = 10.4, 8.7 Hz, 1H), 3.29−3.20 (m, 1H), 3.11−2.92 (m, 2H), 2.77−2.68 (m, 1H), 1.72 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 134.9, 132.8, 131.8, 130.7, 128.8, 128.4, 128.4, 127.9, 127.1, 127.0, 118.9, 65.6, 59.9, 50.0, 44.0, 29.5, 22.5. IR (neat): 2930, 2853, 2242 (C≡N), 1630 (C═O), 1590, 1574, 1494, 1446, 1380, 1281, 1244, 1174, 1123, 1089, 1062, 1036, 940, 910 cm^{-1}. HRMS (ESI) *m*/*z*: calcd for $C_{20}H_{19}N_3O$, 318.1601 ([M + H]$^+$); found, 318.1595 ([M + H]$^+$). $[\alpha]_D^{20}$ −31.6 (*c* 1.0, $CHCl_3$; 62% *ee*). Chiral HPLC (Chiracel OD-H, hexane/isopropanol 9:1, flow rate 0.3 mL/min) retention time: 52 min (minor), 56 min (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C, and ^{19}F NMR spectra; chromatograms for *ee* determination by chiral HPLC; and X-ray data for **2a** and **2e**, including CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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