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Hetero-Diels–Alder Reaction

Enantio- and Diastereoselective Formal Hetero-Diels–Alder Reactions of Trifluoromethylated Enones Catalyzed by Chiral Primary Amines

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Abstract: Enantioselective formal hetero-Diels-Alder reactions of trifluoromethylated enones and 2-amino-1,3-butadienes generated in situ from aliphatic acyclic enones and chiral primary amines are reported. The corresponding tetrahydropyran-4-ones are formed in up to 94% yield and with up to 94% *ee*. The reaction was carried out through a stepwise mechanism, including initial aminocatalytic aldol condensation of 2-amino-1,3-butadiene to the trifluoromethylated carbonyl group followed by an intramolecular oxa-Michael addition. Both NMR investigation and theoretical calculations on the transition state indicate that the protonated tertiary amine could effectively activate the carbonyl group of the trifluoromethyl ketone to promote the addition process through hydrogen-bonding interaction of N–H···F and N–H···O simultaneously, and thus provide a chiral environment for the approach of amino-1,3-butadienes to the activated trifluoromethyl ketone, resulting in high enantioselectivity.

Introduction

Trifluoromethylated organic compounds, as a significant class of halogen compounds, have received increasing attention because of their broad spectrum of intriguing physicochemical properties compared with their isosteric dehalogenated analogues.[1] It is believed that the presence of a trifluoromethyl group in pharmaceutical compounds often enhances and modifies their pharmacological activities.[2] Consequently, efficient approaches that can be used to construct CF_3-bearing organic compounds are of considerable synthetic and biological importance.[3]

The enantioselective hetero-Diels–Alder (HDA) reaction using carbonyl compounds as hetero-dienophiles represents one of the most powerful and straightforward approaches to the effective synthesis of optically active tetrahydropyranone derivatives, which are important structural motifs in a plethora of bioactive natural products and can be transformed into substituted tetrahydropyrans and related derivatives.[4] In most of the HDA reactions, Danishefsky or Brassard's dienes[5] are restricted to act as a diene whether in the metal-based chiral Lewis acid or hydrogen-bond donor catalysts.[6] Recently, asymmetric aminocatalysis has received much attention in organic synthesis[7] and great advances has been made in the HDA reaction (Figure 1) based on the selective activation of carbonyl compounds.[8–9] However, when dienes are generated from enones in situ, oxa-hetero-Diels-Alder reactions using carbonyl groups as dienophiles are difficult.[8h] To form tetrahydropyran derivatives, the use of preformed dienes is often necessary.[10] α,β-Unsaturated enone dienophiles bear two reactive sites, namely, the carbonyl and C=C functionalities, however, the latter structural motif tends to react preferentially in the HDA reaction.[8a–f] To our knowledge, there are no reports of the HDA reaction in which the carbonyl group of α,β-unsaturated enones is employed as a dienophile in aminocatalysis.

Recently, we developed a new family of chiral primary amines, which was found to be effective catalysts in asymmetric aldol condensations.[11] It was found that the enamines generated in situ showed a remarkable propensity for the HDA re-

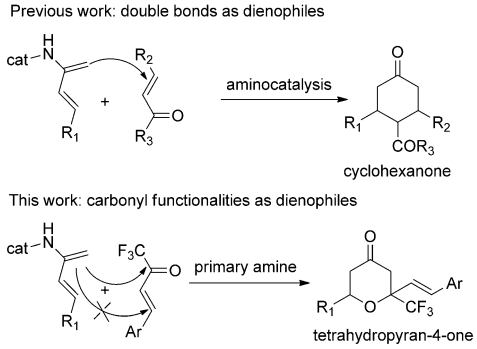

Figure 1. The reactions of 2-amino-1,3-butadienes with α,β-unsaturated enones based on enamine activation.

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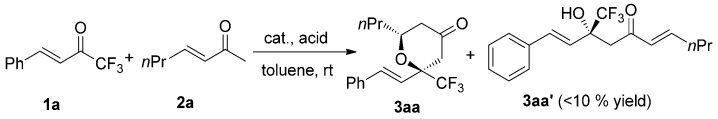
actions with carbonyl functionality (aldol condensation) rather than with the electron-deficient double bond (conjugate addition).[11–12] As part of our continued interest in trifluoromethyl chemistry and aminocatalysis, we reasoned that an amino-butadiene generated in situ from primary amines and aliphatic acyclic enone **2** could selectively react with the carbonyl functionality (aldol–Michael) instead of the double bond (Michael–Michael) of α,β-unsaturated enones **1**. The resulting unique regio- and stereoselective outcome furnishes the corresponding HDA reaction product tetrahydropyran-4-one, which is a key structural motif in a number of natural products;[4] furthermore, the unsaturated double bond can allow further transformations.

Results and Discussion

To explore the proposed process, we undertook an investigation of *N*,*N*-dimethylethylane-1,2-diamine (10 mol%) and trifluoroacetic acid (TFA) (20 mol%) for the HDA reaction of trifluoromethylated enone **1a** with **2a** in dichloromethane at room temperature, affording the HDA product **3aa** in 85% yield as a single diastereoisomer and a trace amount of aldol product after 96 h. Encouraged by this result, a series of chiral primary amine catalysts (Figure 2) and acid additives were examined; the results are summarized in Table 1. Catalyst **I** was first investigated on the basis of the excellent performance in the asymmetric transformations.[11] Unfortunately, only 13% yield was observed, although 83% *ee* was attained after four days (entry 1).

To optimize the procedure further, this model reaction was chosen for a survey of different acids and catalysts. Among these, D-*N*-Boc-phenylglycine[13] proved to be the best choice, providing product **3aa** in 94% yield and 93% *ee* (Table 1, entry 7). The amount of acid had a significant influence on the yield of reaction, but the enantioselectivity was not affected (entries 8 and 9). Several other catalysts were also investigated.

Table 1. Optimization of reaction conditions for the HDA reaction of **1a** and **2a**.



1a **2a** **3aa** **3aa'** (<10 % yield)

Entry[a]	Cat.	Acid	Yield [%][b]	*ee* [%][c]
1	**I**	TFA	13	83 (*R*,*R*)
2	**I**	2-$FC_6H_4CO_2H$	68	82 (*R*,*R*)
3	**I**	4-$NO_2C_6H_4CO_2H$	65	87 (*R*,*R*)
4	**I**	HOAc	55	59 (*R*,*R*)
5	**I**	*N*-Boc-proline	50	80 (*R*,*R*)
6	**I**	L-*N*-Boc-phenylglycine	75	92 (*R*,*R*)
7	**I**	D-*N*-Boc-phenylglycine	94	93 (*R*,*R*)
8[d]	**I**	D-*N*-Boc-phenylglycine	77	92 (*R*,*R*)
9[e]	**I**	D-*N*-Boc-phenylglycine	81	92 (*R*,*R*)
10	**II**	D-*N*-Boc-Phenylglycine	90	54 (*R*,*R*)
11	**III**	D-*N*-Boc-phenylglycine	44	88 (*R*,*R*)
12	**IV**	D-*N*-Boc-Phrnylglycine	54	81 (*S*,*S*)
13	**V**	D-*N*-Boc-phenylglycine	63	85 (*R*,*R*)
14	**VI**	D-*N*-Boc-phenylglycine	59	86 (*S*,*S*)

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.5 mmol), amine catalyst (10 mol%), acid (20 mol%), toluene, RT, 48–96 h. [b] Isolated yield and a single diastereomer was observed unless indicated otherwise. [c] Determined by HPLC analysis. [d] 15 mol% acid employed. [e] 25 mol% acid used.

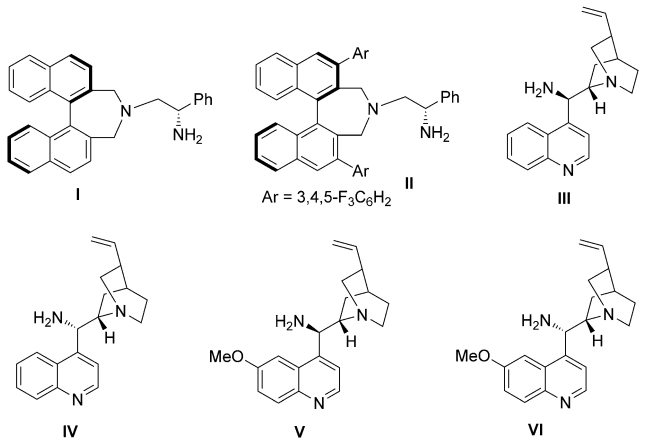
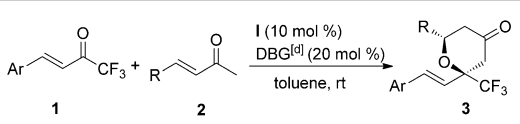


Figure 2. The chiral primary amines that were screened in this work.

For instance, primary amine **II**, with a bulky 3,4,5-trifluorophenyl group in the 3,3′-position of **I**, afforded the product **3aa** with high yield but with low enantioselectivity (entry 10). Cinchona alkaloid derived chiral primary amines **III**–**VI** provided **3aa** in 44–63% yield and with 81–88% *ee* (entries 11–14). Solvents screening indicated that toluene was the optimal choice in terms of yields and enantioselectivities (see the Supporting Information). It should be noted that only one isomer was obtained in all cases.

With the optimized conditions in hand, the substrate scope of the reaction was examined by using a variety of α,β-unsaturated trifluoromethyl ketones **1** and acyclic aliphatic enones **2**; representative results are listed in Table 2. All trifluoromethyl enones reacted with enone **2a** to afford the desired heterocyclic products **3aa**–**ma** (entries 1–13). It was found that the electronic nature of substituents on the phenyl ring had a significant effect on the reaction. Electron-withdrawing groups were beneficial for achieving good enantioselectivities (entries 1–10); in contrast, electron-donating groups such as methyl or methoxy groups on the phenyl ring delivered decreased enantioselectivity (entries 11–12). The substrates with heteroaromatic rings such as furyl at the β-position of the enones also proceeded smoothly in the HDA reaction (entry 13). Several other acyclic aliphatic enones were also tested. For example, (*E*)-5-methylhex-3-en-2-one (**2b**) reacted with **1a**–**g**, providing the corresponding products **3ab**–**gb** in 77–83% yield and with 85–92% *ee* (entries 14–20). (*E*)-Dec-3-en-2-one (**2c**) was also compatible under the standard conditions (entries 21–22). However, enone **2d**, with an aromatic phenyl substitution at the β-position, was completely unreactive, which may be attributed to the alteration in the electronic density resulting from the conjugation effect (entry 23).

Table 2. Enantioselective HDA reaction.

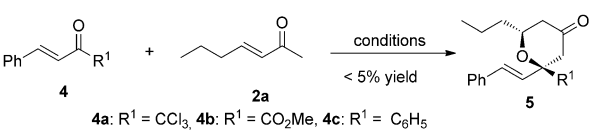


1 2 3

Entry[a]	Ar	R	3	Yield [%][b]	*ee* [%][c]
1	Ph	*n*Pr	**3aa**	94	93
2	2-BrPh	*n*Pr	**3ba**	81	92
3	4-BrPh	*n*Pr	**3ca**	75	90
4	3-BrPh	*n*Pr	**3da**	73	90
5	4-ClPh	*n*Pr	**3ea**	65	90
6	3-ClPh	*n*Pr	**3fa**	76	90
7	4-FPh	*n*Pr	**3ga**	67	94
8	4-NO_2Ph	*n*Pr	**3ha**	83	92
9	2-Napth	*n*Pr	**3ia**	74	93
10	4-CF_3Ph	*n*Pr	**3ja**	66	92
11	4-CH_3Ph	*n*Pr	**3ka**	50	74
12	3-MeOPh	*n*Pr	**3la**	64	50
13	2-Furyl	*n*Pr	**3ma**	70	76
14	Ph	*i*Pr	**3ab**	80	90
15	*o*-BrPh	*i*Pr	**3bb**	81	90
16	4-BrPh	*i*Pr	**3cb**	81	85
17	3-BrPh	*i*Pr	**3db**	80	87
18	4-ClPh	*i*Pr	**3eb**	77	85
19	3-ClPh	*i*Pr	**3fb**	79	92
20	4-FPh	*i*Pr	**3gb**	83	91
21	Ph	*n*Hex	**3ac**	73	87
22	2-BrPh	*n*Hex	**3bc**	89	90
23	Ph	Ph	**3ad**	–	–

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.5 mmol), **I** (10 mol%), DBG (20 mol%), RT. [b] Isolated yields and a single diastereomer was observed unless otherwise stated. [c] Determined by HPLC analysis. [d] DBG = D-Boc-phenylglycine.

Other enones without α-H were also investigated. Trichloromethyl enone **4a**, β,γ-unsaturated α-ketoester **4b**, and chalcone **4c** were not reactive under identical conditions after five days (Scheme 1). Based on these observations, we envisioned that the trifluoromethyl group plays a significant role in accelerating the reaction through the interaction of the F–H bond of enones **1** with the catalyst. To account for the phenomena observed in the experiments, we conducted ^{1}F NMR analysis (Figure 3). The chemical shift of fluorine nucleus for **1a** was measured at −77.6 ppm by using deuterated toluene as the solvent (Figure 3, a). Addition of a co-catalyst D-*N*-Boc- phenylglycine (1 equiv with respect to **1a**) resulted in no apparent changes (Figure 3, b). However, injection of chiral amine **I** generated a new signal at −67.2 ppm (Figure 3, c). The signal indicates that an interaction between enone **1a** and the catalyst occurred. In the absence of enone **2a**, the signal remained unchanged; however, addition of **2a** resulted in the appearance of the F signal at higher field (Figure 3, d).



4 2a 5

4a: R^1 = CCl_3, **4b**: R^1 = CO_2Me, **4c**: R^1 = C_6H_5

Scheme 1. The investigation of other α,β-unsaturated enones bearing no α-H.

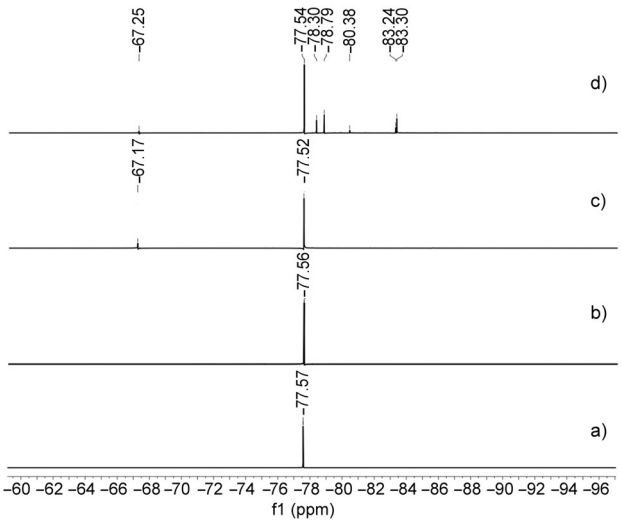
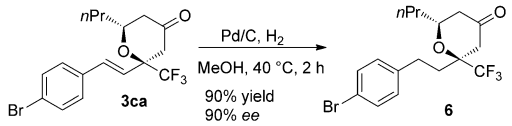


Figure 3. Fluorine NMR spectra: a) Trifluoromethyl enone **1a** (0.01 mmol); b) **1a** (0.01 mmol) and D-*N*-Boc-phenylglycine (0.01 mmol); c) **1a** (0.01 mmol), amine **I** (0.01 mmol) and D-*N*-Boc-phenylglycine (0.01 mmol); d) **1a** (0.01 mmol), amine **I** (0.01 mmol), D-*N*-Boc-phenylglycine (0.01 mmol) and **2a** (0.01 mmol). Solvent: deuterated toluene (1 mL).

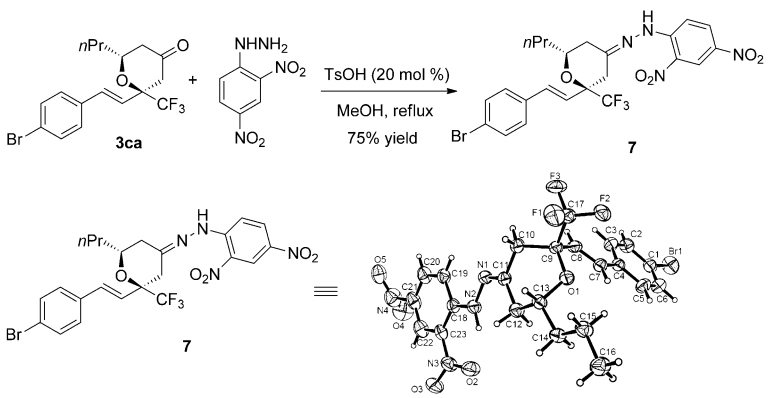
With the successful construction of tetrahydropyran-4-ones, we turned our attention to performing further transformations of cycloadducts **3** into valuable compounds. As illustrated in Scheme 2, hydrogenation of the double bond in **3ca** by Pd/C-catalysis produced adduct **6** in 90% yield, with no erosion of enantioselectivity.[14]



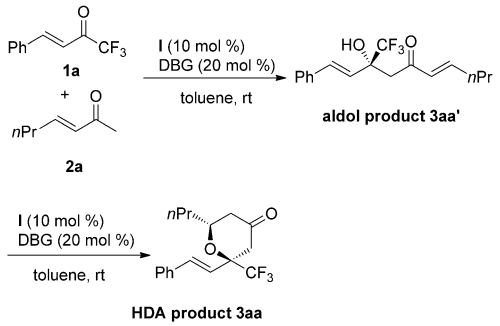
Scheme 2. Transformation of product **3ca**.

All the HDA products **3** were formed as oils. To determine the absolute configuration, **3ca** was transformed into a solid derivative. The product **3ca** was condensed with (2,4-dinitrophenyl)hydrazine in the presence of 20 mol% TsOH by using methanol as solvent. The corresponding hydrazone **7** was isolated in 75% yield, with no erosion in enantioselectivity (Scheme 3). After recrystallization from methanol, a suitable crystal for X-ray diffraction was obtained and the absolute configuration of **7** was thus assigned to be (2*R*,6*R*).[15]

Apart from the HDA products, aldol adducts that resulted from the aldol addition of 2-amino-1,3-butadienes to the carbonyl functionality of **1a** were also observed, albeit with low yield (<10%). Simultaneously, it was found that the aldol product **3aa**′ could be transformed into HDA products under the same reaction conditions (see the Supporting Information). Based on the experimental results detailed above, we proposed a stepwise aldol–Michael reaction pathway (Scheme 4).



Scheme 3. Determination of the absolute configuration of the stereogenic centers in **3ca**.



Scheme 4. Stepwise reaction sequence.

To further elucidate the mechanism of the reaction, theoretical calculations were performed on the plausible transition states (TS) by using the B3LYP/6-31(d) method,[16] as implemented in the Gaussian 09 program.[17] The located stable TS structures are depicted in Figure 4. The protonated tertiary amine in the key enamine intermediate could act as a hydrogen-bond (HB) donor to facilitate binding of enone **1a** to the enamine through hydrogen-bonding interactions and simultaneously activate the carbonyl group of **1a** to promote nucleophilic addition of the enamine to the carbonyl group of **1a**. Transition states *R*-TS-1 and *R*-TS-2 both involve the nucleophilic addition of 2-amino-1, 3-butadiene, formed in situ, to the carbonyl group of **1a** from the *Si* face, whereas transition states *S*-TS-1 and *S*-TS-2 concern nucleophilic attack from the *Re* face. Careful inspection of Figure 4 reveals a few notable geometric features. In transition states *R*-TS-1 and *S*-TS-1, there is an almost eclipsed conformation for the addition. The concurrent hydrogen-bonding interactions of N–H···O and N–H···F form a five-membered ring structure, which contributes to the high stability of transition states *R*-TS-1 and *S*-TS-1. The hydrogen-bonding interaction of N–H···F, however, is missing in transition states *R*-TS-2 and *S*-TS-2. Taken together, transition states *R*-TS-1 and *S*-TS-1 are predicted to be more favorable than transition states *R*-TS-2 and *S*-TS-2, which fits in well with the energetics. Transition state *R*-TS-1 is 8.0 kcal mol^{-1} lower in both enthalpy and free energy than transition state *R*-TS-2, and transition state *S*-TS-1 is 1.1 kcal mol^{-1} lower in enthalpy and 0.2 kcal mol^{-1} lower in free energy than transition state *S*-TS-2. Furthermore, compared with transition state *S*-TS-1, transition state *R*-TS-1 is 3 kcal mol^{-1} lower in enthalpy and 3.7 kcal mol^{-1} lower in free energy and is therefore the most plausible transition state reported for the nucleophilic addition of enamine to the carbonyl group of **1a**, providing the aldol product in *R*-configuration. Subsequent intramolecular oxa-Michael addition from the less congested *Re*-face of azadiene intermediate affords the experimentally desired (*R*,*R*)-tetrahydropyran-4-ones **3**. As a consequence, the hydrogen-bonding interaction of N–H···F facilitates the nucleophilic addition of enamine to the carbonyl group. Other electron-deficient methyl enones rather than CF_3 such as **4a** and **4b** are therefore not reactive.

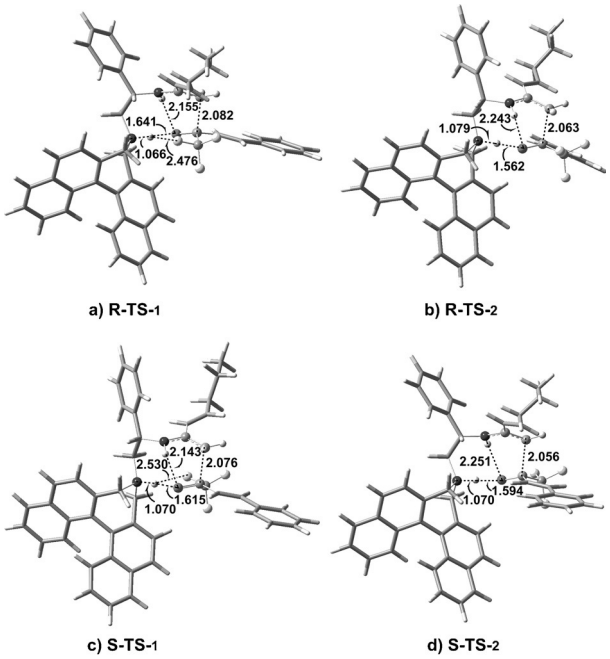


Figure 4. Located transition-state structures in the enantioselective aldol reaction by using the Bg3LYP/6-31(d) method; distances are in Å; relative enthalpies and Gibbs free energies [kcal mol^{-1}], respectively, are as follows: a) *R*-TS-1, 0.00 and 0.00; b) *R*-TS-2, 8.0 and 8.0; c) *S*-TS-1, 3.0 and 3.7; d) *S*-TS-2, 4.1 and 3.9.

Conclusion

We have disclosed a set of primary amine catalyzed formal hetero-Diels-Alder reactions of the carbonyl group in electron-deficient trifluoromethylated α,β-unsaturated enones **1** and enolizable acyclic aliphatic enones **2**. The corresponding optically enriched tetrahydropyran-4-ones **3** were obtained in up to 94% yield and with 94% *ee*. The reaction was carried out in

a stepwise aldol–Michael reaction. Mechanistic studies revealed that the protonated tertiary amine activates the carbonyl group of the trifluoromethyl ketone through hydrogen-bonding interaction of N–H···O and N–H···F simultaneously and provides a chiral environment that leads to high enantioselectivities of the reaction.

Experimental Section

General information

All reactions were carried out in oven-dried glassware with magnetic stirring. All the reagents were obtained from commercial supplier and were used as received without further purification unless otherwise noted. Solvents used in the reactions were distilled from appropriate drying agents prior to use. ^{1}H and ^{13}C NMR spectra were recorded respectively at 400 and 100 MHz with a Bruker AVANCE 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR signals are reported as δ units in parts per million (ppm) downfield from TMS ($\delta = 0.0$ ppm) with $CDCl_3$ ($\delta = 7.26$ ppm, singlet) resonance as the internal standard. The signal of H_2O in $CDCl_3$ is $\delta = 1.65$ ppm (singlet). The multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublets of doublet) or m (multiplet). The number of protons (*n*) for a given resonance is indicated by *n*H. Coupling constants (*J*) for ^{1}H NMR are reported in Hz and refer to apparent peak multiplicities. ^{13}C NMR shifts are reported as δ units of parts per million (ppm) downfield from TMS ($\delta = 0.0$ ppm) and relative to the signal of $CDCl_3$ ($\delta = 77.0$ ppm, triplet). Optical rotations were measured in the indicated solvents with a PerkinElmer polarimeter (Polartronic MH8) with a 10 cm cell (*c* given in g/100 mL). Flash chromatography was conducted on silica gel (300–400 mesh) with distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. Enantiomeric excess (*ee*) were determined by HPLC analysis with a Shimadzu LC-20A, employing a Daicel Chiralcel AD-H, AS-H, OD-H or IA-H column (250×4.6 mm). High-resolution mass spectra were obtained with a Bruker Daltonics micrOTOF-Q II spectrometer in ESI mode. The relative and absolute configuration of **6** were assigned based on X-ray analysis and the other cycloaddition products were assigned by analogy.

Typical procedure for the formal HDA reactions

To a dried tube was added catalyst **I** (4.2 mg, 0.01 mmol) and D-Boc-phenylglycine (5.0 mg, 0.02 mmol), then toluene (0.5 mL) was added. The mixture was stirred at RT for 15 min until a white turbidity was observed, then α,β-unsaturated trifluoromethyl ketone **1a** (0.1 mmol), aliphatic enone **2a** (0.5 mmol), and toluene (0.5 mL) were added. The reaction mixture was stirred at RT until the reaction was complete (monitored by TLC), the solvent was then removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 120:1) to give the corresponding HDA product **3aa**. Yield: 94%; colorless oil; $[\alpha]_D^{27} = 9.7$ ($c = 0.23$, CH_2Cl_2); 93% *ee*, determined by HPLC analysis (Chiralpak AS-H column; 2% IPA in hexane; rate: 1.0 mL min^{-1}; 254 nm): $t_R = 10.7$ (major), 12.3 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–7.41 (m, 2H), 7.38–7.29 (m, 3H), 6.91 (d, $J = 15.9$ Hz, 1H), 6.15 (d, $J = 15.9$ Hz, 1H), 4.41–4.36 (m, 1H), 3.06 (d, $J = 15.5$ Hz, 1H), 2.66 (d, $J = 15.6$ Hz, 1H), 2.52 (dd, $J = 17.1$, 2.8 Hz, 1H), 2.32 (dd, $J = 17.0$, 11.6 Hz, 1H), 1.84–1.72 (m, 1H), 1.66–1.44 (m, 3H), 1.02 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 203.6, 135.4, 133.4, 129.4, 128.7, 128.6, 127.0, 125.1 (q, $J =$ 288.5 Hz), 124.9, 77.8 (q, $J = 28.6$ Hz), 73.1, 46.0, 43.1, 38.2, 18.3, 13.8 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{20}F_3O_2$ 313.1410 $[M+H]^+$; found 313.1408.

(2*S*,6*S*)-6-Isopropyl-2-phenethyl-2-(trifluoromethyl)tetrahydro-4*H*-pyran-4-one (6)

Palladium/charcoal (10%, 2 mg) was added to a solution of **3ca** (20 mg) in methanol (2 mL), and the reaction mixture was stirred and warmed to 40 °C under a balloon of hydrogen for 2 h. The mixture was then filtered through a bed of Celite and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 100:1) to provide the desired compound **6**. Yield: 90%; yellow oil; $[\alpha]_D^{24} = -22.1$ ($c = 0.15$, CH_2Cl_2); 90% *ee*, determined by HPLC analysis (Chiralpak OD-H column; 10% *i*PrOH in hexane; rate: 1.0 mL min^{-1}; 210 nm): $t_R = 9.5$ (major), 14.7 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$ (t, $J = 7.4$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 3H), 4.23 (br s, 1H), 2.93–2.63 (m, 3H), 2.59–2.42 (m, 2H), 2.26 (dd, $J = 16.4$, 11.5 Hz, 1H), 2.18–2.15 (m, 1H), 1.91 (td, $J =$ 12.9, 5.3 Hz, 1H), 1.72–1.63 (m, 1H), 1.59–1.43 (m, 3H), 0.97 ppm (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 204.5$, 140.9, 130.6, 128.6, 128.3, 127.7, 126.2, 124.8, 77.3, 77.0, 76.7, 72.8, 46.1, 42.4, 38.3, 38.2, 28.8, 18.2, 13.8 ppm; HRMS (ESI): *m/z* calcd for $C_{17}H_{21}BrF_3O_2$ 393.0698 $[M+H]^+$; found 393.0696.

(*Z*)-1-{(2*R*,6*R*)-2-[(*E*)-4-Bromostyryl]-6-propyl-2-(trifluoromethyl)tetrahydro-4*H*-pyran-4-ylidene}-2-(2,4-dinitrophenyl)hydrazine (7)

p-TsOH (7 mg, 0.04 mmol) followed by 2,4-dinitrophenyl hydrazine (119 mg, 0.6 mmol) were added to a solution of **3ca** (78.3 mg, 0.2 mmol) in methanol (7 mL). The reaction was heated to reflux until the reaction was complete (monitored by TLC). The reaction mixture was cooled to RT and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 30:1–20:1) to provide **7**. Yield: 75%; yellow solid; m.p. 151–153 °C; $[\alpha]_D^{24} = 14.8$ ($c = 0.45$, CH_2Cl_2); >99% *ee* (after recrystallization), determined by HPLC analysis (Chiralpak OD-H column; 4% EtOH in hexane; rate: 1.0 mL min^{-1}; 254 nm): $t_R = 40.7$ (minor), 44.9 min (major); ^{1}HNMR (400 MHz, $CDCl_3$): $\delta = 11.00$ (s, 1H), 9.11 (d, $J = 2.4$ Hz, 1H), 8.32 (dd, $J = 9.5$, 2.3 Hz, 1H), 7.94 (d, $J = 9.6$ Hz, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8,5$ Hz, 2H), 6.81 (d, $J = 15.7$ Hz, 1H), 6.13 (d, $J =$ 15.8 Hz, 1H), 4.39–4.34 (m, 1H), 3.30 (d, $J = 15.1$ Hz, 1H), 2.87 (d, $J = 15.1$ Hz, 1H), 2.67 (d, $J = 16.1$ Hz, 1H), 2.38 (dd, $J = 17.4$, 11.68 Hz, 1H), 1.82–1.70 (m, 1H), 1.64–1.44 (m, 3H), 1.04 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.2$, 144.8, 138.4, 134.4, 132.8, 131.8, 129.6, 128.4, 125.5, 116.4, 77.3 (q, $J = 28.3$ Hz), 71.3, 37.7, 34.7, 33.8, 18.5, 13.8 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{22}BrF_3N_4O_5$ 571.0804 $[M+H]^+$; found 571.0798.

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