Asymmetric α-Alkylation of β-Ketocarbonyls *via* Direct Phenacyl Bromide Photolysis by Chiral Primary Amine

Wen-Zhao Zhang,[a] Yunbo Zhu,[a] Long Zhang [ab] and Sanzhong Luo*[ab]

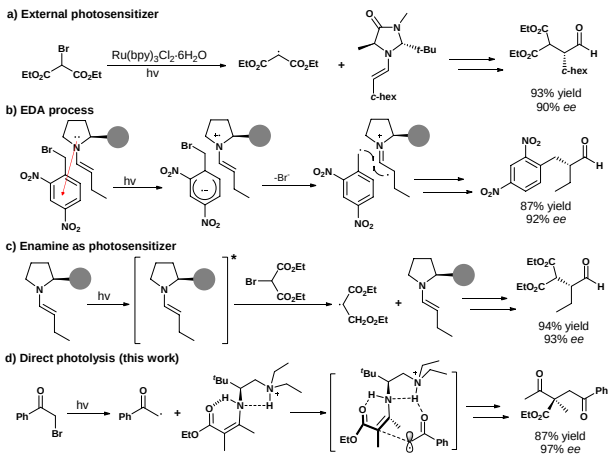
ABSTRACT Enantioselective α-photoalkylation of β-ketocarbonyls without any external photosensitizer was described in this work. The photoalkylation reactions, enabled solely by a chiral primary amine catalyst, provided convenient constructions of all-carbon quaternary stereocenters with good activity and high enantioselectivity. Mechanism studies revealed a direct photolytic radical chain process under visible light irradiation.

KEYWORDS photolysis, aminocatalysis, asymmetric alkylation, β-ketocarbonyls

Introduction

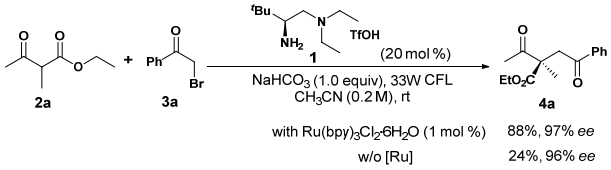
Catalytic asymmetric photochemical reactions have received increasing attentions echoing the revival of visible light photochemistry in organic synthesis.[[1]] One of the leading strategies is the merging of photochemical process with the established enantioselective catalytic pathways.[[2]] Recently, enantioselective aminocatalysis has become an enabling strategy for stereocontrol in photochemical transformations.[[3]] The combination of known aminocatalysts with photoredox catalysts has shown to enable enantioselective radical alkylation reactions (Scheme 1a).[[3]a] Later on, it was found by Melchiorre that external photoredox catalyst was not necessary and distinctive electron-donor activation involving *in-situ* formed enamine could initialize the radical chain alkylation process (Scheme 1b).[[3]k] The catalytic enamine intermediate could also serve as transient photosensitizer to facilitate the photoalkylation reaction (Scheme 1c).[[3]m] Herein, we reported direct photolysis of substrate without external photocatalyst could also be successfully coupled with enamine cycle to facilitate a highly enantioselective photoalkylation process (Scheme 1d).

Scheme 1 Mechanisms of asymmetric aminocatalysis photoreaction



Enantioselective construction of all-carbon quaternary centers remains a daunting challenge in asymmetric catalysis. Asymmetric alkylation of tri-substituted enolates[[4]] or enamines[[3]g],[[5]] is one of the most straightforward approach for this end. Lately, we have explored enamine catalysis with α-branched aldehydes and ketones for the asymmetric synthesis of quaternary centers by chiral primary amine.[6] The combined chiral primary amine/photoredox Ruthium catalysis has been developed to promote a photoradical alkylation of β-ketocarbonyls with excellent stereocontrol (Scheme 2).[[3]g],[[6]] During this study, we found a sole chiral primary amine was also able to promote the reaction in the absence of photoredox catalyst. The desired photoalkylation adduct could be obtained in 24% yield and with essentially maintained enantioselectivity (96% *ee*, Scheme 2). On the basis of Melchiorre photoredox catalyst-free precedence, we have further explored this chrial primary amine-photoalkylation system. Herein, we reported a mechanistically distinctive photolytic process for the enamine photoalkylation reactions, in which the expensive ruthenium photosensitizer is no longer needed (Scheme 1d).

Scheme 2 Previous reported results

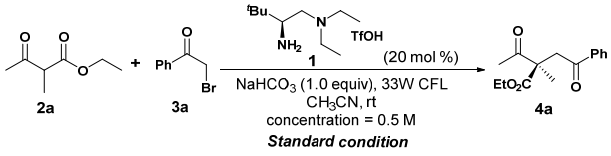


Results and Discussion

Results

We initially worked to further improve the reactivity. In a pilot experiment between β-ketocarbonyl **2a** and phenacyl bromide **3a**, it was quickly found out that simply increasing the reaction concentration from 0.2 M to 0.5 M would lead to significant enhancement of the reactivity (Table 1, entry 1). Under fluorescence bulb irradiation, the sole use of our bench mark primary amine catalyst **1** gave the desired product in 87% yield and 97% *ee*. The reactivity was comparable to primary amine **1**/[Ru] dual catalytic procedure (88% yield, 97% *ee*, Scheme 2). A number of experiments were then conducted to uncover the underlying mechanism for the photocatalyst free system.

Table 1 Improved reaction and control experiments[a]



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Entry	Light	Band pass	Yield(%)[c]	*ee*[d]
1	33W CFL	No	87	97
2	15W 395nm LEDs	No	85	94
3	3W Blue LEDs	No	25	95
4	33W CFL	400nm	13	97
5	33W CFL	470nm	Trace	--
6[b]	33W CFL	No	20	0

[a]Reactions were performed at room temperature in 0.4 mL MeCN, with **2a** (0.8 mmol), **3a** (0.2 mmol), **1** (20 mol %), $NaHCO_3$ (1 equiv) and different light and different band pass under nitrogen, 48 h. [b]Without **1**. [c]Yield of isolated product. [d]Determined bu HPLC analysis.

Light sources were then tested in order to reveal the light responsive behaviors (Table 1, entries 1-4). The use of 395nm LED lead to similar outcome (entry 2), however, the production yield went down sharply when blue LED was applied (entry 3). The reaction under CFL with a 400nm band pass (removal of light whose wavelength is less than 400nm) gave only 13% yield with maintaining enantioselectivity (entry 4), and the 470 nm band pass reaction resulted in virtually no reaction (entry 5). These results verified the light promoting nature of the current reaction and that the reaction is mostly effective under <400 nm light irradiation.

UV-Visible spectrum were then investigated (Scheme 3). None of the reactants including the enamine intermediate **6**·TfOH (preformed) showed noticeable absorption beyond 350 nm under typical dilute conditions (Scheme 3, B). In addition, ketoseter **2a** alone or together with aminocatalyst **1** showed no obvious absorption beyond 370 nm (Scheme 3, B). Under the reaction concentration (>0.5 M), phenacyl bromide **3a** exhibited significant absorption @400 nm (Scheme 2, A). No obvious red shift was observed when **2a** was added. In the presence of **2a** and aminocatalyst **1**, a slightly red shift was noted, suggesting the likely existence of an EDA complex between **3a** and enamine intermediate. However, this EDA complex, even if existed, should play a minor role as the reaction barely proceeded under a 400 nm band pass (Table 1, entry 4). Another possible working mechanism is that the *in-situ* formed enamine intermediate serve as a photosensitizer. Provided with strong absorption of phenacyl bromide above 400 nm and its high concentration (0. 5 M), this mechanism is unlikely and can be excluded when considering the low concentration of the *in-situ* formed enamine and its very weak absorption above 370 nm under the reaction conditions. In this context, direct photolysis of phenacyl bromide was considered as the major working mechanism.

Radical quenching experiment was also conducted and the addition of TEMPO was found to completely inhibit the reaction. We could isolate a phenacyl-TEMPO adduct **5** from the quenched reaction mixture, adding support to the radical mechanism (Table 2, entry 1). The same adduct could also be isolated with 32% yield in the absence of aminocatalyst (entry 2). Inorganic base $NaHCO_3$ showed no obvious effect on the yield of **5** (entry 3). The quenching process still led to 24% yield of **5** in the absence of both aminocatalyst and inorganic base (entry 4). These results indicated that neither aminocatalyst nor its derived intermediate is involved in the generation of phenacyl radical. The involvement of enolate could also be excluded on the basis of neglectable effect of base. In sharp contrast, no quenching adduct was detected when conducting in dark (Table 2, entry 5), supporting a photolytic process for radical generation. In fact, direct photolytic hemolysis of phenacyl bromide is known.[8] However, such a working mode has not been disclosed in the context of asymmetric aminocatalysis.

Scheme 3 Mechanisms of asymmetric aminocatalysis photoreaction[a]

[a]UV-Visible spectrum of different components. A: Optical absorption spectra, recorded in MeCN in 1 cm path quartz cuvettes, [**2a**] = 2 M, [**3a**] = 0.5 M, and [**1**] = 0.1 M. B: Optical absorption spectra, recorded in MeCN in 1 cm path quartz cuvettes, [**2a**] = 2 × 10-5 M, [**3a**] = 2 × 10-5 M, [**1**] =4 × 10-6 M and [**enamine**] = 4 × 10-6 M

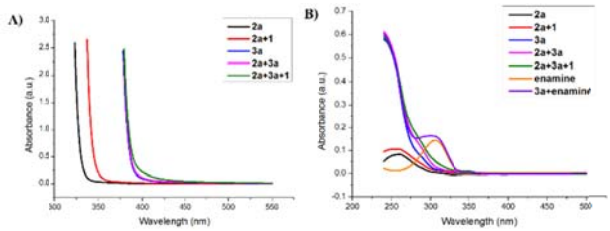
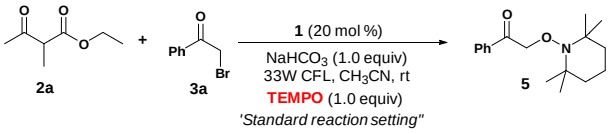


Table 2. Radical quenching experiments[a]

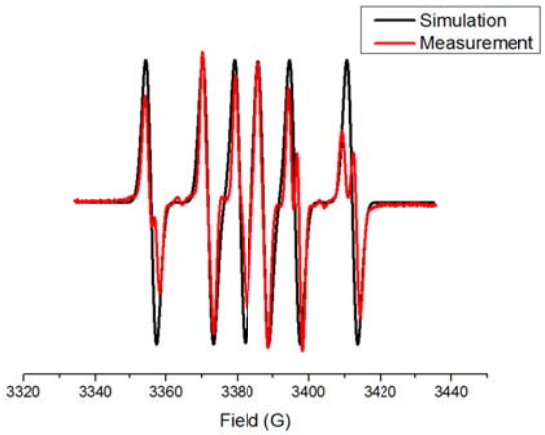


Entry	Light	**1**	$NaHCO_3$	Yield(%) of **5**[c]
1	33W CFL	20 mol %	1.0 eq	26
2	33W CFL	No	1.0 eq	32
3	33W CFL	20 mol %	no	27
4[b]	33W CFL	no	no	24
5	No	20 mol %	1.0 eq	no reaction

[a]Standard reaction setting: the reaction was performed at room temperature in 0.4 mL MeCN, with **2a** (0.8 mmol), **3a** (0.2 mmol), $NaHCO_3$ (1 equiv), TEMPO (1 equiv.) and 33 W CFL under nitrogen, 48 h. [b]phenacyl bromide only. [c]Yield of isolated product.

We next use EPR to directly detect the radical specie in the reaction mixture. Without any light irradiation, the reaction mixture remained EPR silent. Upon CFL irradiation, a strong EPR signal, characteristic of carbon-center radical species, could be observed (Scheme 4), confirming unequivocally radical nature of the reaction. This radical signal can also be confirmed by EPR simulation. We also measured the quantum yield (Φ) of this reaction under 395nm LED. In two parallel experiments, the results are 17 and 20, respectively, indicating a radical chain process (SI).[3m]

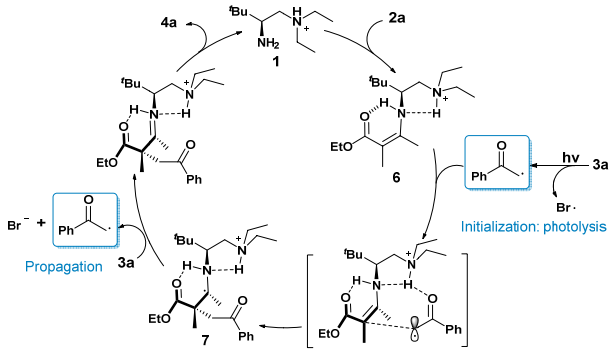
Scheme 4 EPR spectra of catalytic system[a]



[a]In MeCN. Conditions: [**2a**] = 2 M, [**3**a] = 0.5 M, and [**1**] = 0.1 M, 9.511 GHz microwave frequency, 10.11 mW microwave power, 2 G modulation amplitude, and 40.96 ms time constant.

Based on the above evidences, a simple photolytic radical chain process was proposed for the current reaction (Scheme 5). The reaction was initialized by photolysis of **3a** to generate a phenacyl radical.[[8]] This phenacyl radical will attack the in-situ generated enamine **6** and the protonated N-H bonding dictates the facial selection in this radical addition step. Considering the high reduction potential of **3a**(E_p^{red} = -1.35 V),[[7]] reductive quenching of **3a** by the resulted amino radical **7** would regenerate phenacyl radical for propagation[3m],[**Error! Reference source not found.**] and complete the aminocatalytic cycle upon hydrolysis.

Scheme 5 Proposed mechanism



The scope of this photocatalyst-free system was next explored (Table 3). Different ester moiety on the ketoester substrates were tolerated to give good yields and high enantioselectivity (Table 3, **4a**-**b**). α-Acetybutyrolactone reacted well under present conditions with 99% yield and 77% *ee* (**4r**). Cyclic β-ketoesters are also suitable for this reaction, and the activity of five-member ring ester is even better than **2a** with high enantioselectivity (**4g**-**m**). Six- and seven-membered cyclic ketoesters worked equally well in the reactions (**4m**-**p**). Acyclic 1,3-diketones could be applied with high enantioselectivity (**4s**-**v**). The reaction could be generally applied with different substituted phenacyl bromides, bearing either electron withdrawing group or electron donating group (**4c**-**f** and **4g**-**m**).[10] β-Ketoamides have also been examined in the current protocol, showing unfortunately low productivity and complicated reaction mixture, likely a result of interference of the amide group. The reaction with unsaturated ethyl acetoacetate was examined, showing good reactivity but no enantioselectivity due to the facile enol-keto tautomerization of the obtained mono-alkylated product.

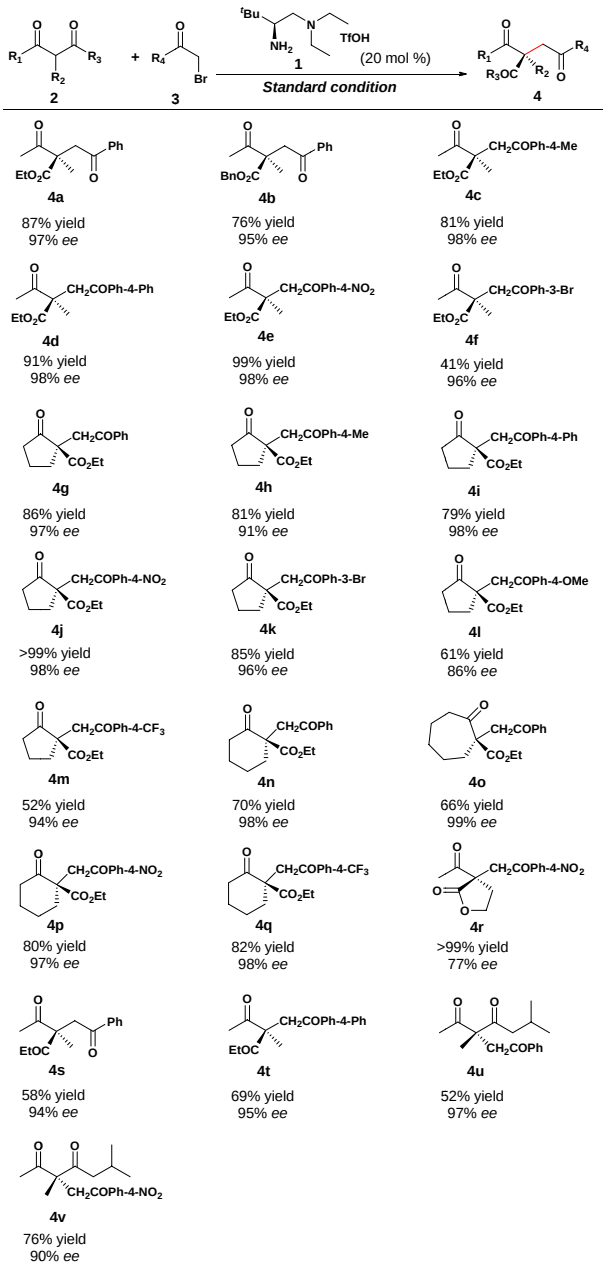


Table 3. Scope of β-ketocarbonyls and α-bromocarbonyls[a]

[a]All reactions were performed at room temperature in 0.4 mL MeCN, with **2** (0.8 mmol), **3** (0.2 mmol), **1** (20 mol %), $NaHCO_3$ (1 equiv) and 33 W CFL under nitrogen, 48 h. Yield of isolated product. Determined by HPLC analysis.

Conclusions

In conclusion, we have achieved an enantioselective α-photoalkylation of β-ketocarbonyls under household CFL light source without external photosensitizer. This reaction enables to create asymmetric all carbon quandary centers with good yields and high enantioselectivity for a decent range of substrate scope.

Mechanism studies verify a photolytic radical chain process.

Experimental section

Materials: Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[11] All solvents were purified according to the method of Grubbs.[12] The corresponding bromides **3**, β-ketoesters **2a**, **2g**, **2n** and **2r** were commercially available. β-ketoesters **2b** and 1,3-diketones **2u** were prepared by alkylation of the corresponding α-unsubstituted β-ketoesters with alkyl iodide.[13] 1,3-Diketones **2s**[14] and cyclic β-ketoesters **2p**[15] were prepared according to the corresponding literature.

General procedure for the synthesis of alkylation product: An oven-dried 10 mL schlenk tube was charged with primary-tertiary diamine **1** (20 mol %), the corresponding bromide **3** (0.2 mmol, 1 equiv), ß-ketocarbonyls (if solid) (0.8 mmol, 4 equiv) and $NaHCO_3$ (1 equiv). The tube was purged with a stream of nitrogen, 0.4 mL of dry CH_3CN (with β-ketocarbonyls (if liquid), 0.8 mmol) was added via syringe. The resultant mixture was degassed three times. Then the tube was placed approximately 3 cm to a 33w CFL and stirred at room temperature. After the reaction was complete (TLC analysis, about 48h). Solvent was removed and the residue was purified directly by silica gel column to give the target products.

Analytical data for products

4a: 87% yield, 97% *ee*. $[\alpha]_D^{25}$ = 46.3 (c = 1.58, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 5:95, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 22.86 min (major), 28.61 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (d, J = 7.0 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.62 (q, 2H), 2.33 (s, 3H), 1.56 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 205.62 , 197.10 , 172.33 , 136.55 , 133.36 , 128.62 , 128.05 , 61.59 , 57.28 , 44.60 , 26.47 , 20.73 , 13.95 . IR data was reported previously.[3g] HRMS (ESI) calcd for $C_{15}H_{18}O_4Na^+$: 285.1097, found 285.1095.

4b: 76% yield, 95% *ee*. $[\alpha]_D^{25}$ = 41.8 (c = 1.95, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 35.14 min (major), 43.16 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.95 (d, J = 8.0 Hz, 2H), 7.57 (t, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 3.5 Hz, 5H), 5.19 (q, 2H), 3.65 (q, 2H), 2.26 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 205.34 , 197.07 , 172.18 , 136.49 , 135.35 , 133.41 , 128.63 , 128.56 , 128.36 , 128.24 , 128.09 , 67.34 , 57.36 , 44.63 , 26.49 , 20.75 . IR data was reported previously. [3g] HRMS (ESI) calcd for $C_{20}H_{20}O_4Na^+$: 347.1254, found 347.1253.

4c: 81% yield, 98% *ee*. $[\alpha]_D^{25}$ = 35.2 (c = 0.80, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 250 nm, retention time: 15.94 min (major), 17.58 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.86 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.61 (q, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 1.56 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 205.70 , 196.70 , 172.40 , 144.21 , 134.11 , 129.29 , 128.18 , 61.56 , 57.27 , 44.50 , 26.48 , 21.67 , 20.71 , 13.96 . IR data was reported previously. [3g] HRMS (ESI) calcd for $C^{16}H^{20}O^4Na^+$: 299.1254, found 299.1254.

4d: 91% yield, 98% *ee*. $[\alpha]_D^{25}$ = 25.5 (c = 2.52, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 282 nm, retention time: 28.14 min (major), 32.47 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.04 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.67 (q, 2H), 2.35 (s, 3H), 1.59 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 205.64 , 196.69 , 172.36 , 146.04 , 139.78 , 135.27 , 128.98 , 128.68 , 128.30 , 127.28 , 127.26 , 61.62 , 57.34 , 44.64 , 26.50 , 20.77 , 13.99 . IR data was reported previously. [3g] HRMS (ESI) calcd for $C_{21}H_{22}O_4Na^+$: 361.1410, found 361.1409.

4e: 99% yield, 98% *ee*. $[\alpha]_D^{25}$ = 35.1 (c = 2.30, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 260 nm, retention time: 32.98 min (major), 44.45 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.30 (d, 2H), 8.10 (d, J = 8.7 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.60 (q, 2H), 2.34 (s, 3H), 1.58 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 205.34 , 195.82 , 171.97 , 150.44 , 140.97 , 129.11 , 123.86 , 61.81 , 57.45 , 44.95 , 26.52 , 20.90 , 13.96 . IR data was reported.[3g] HRMS (APCI) calcd for $C_{15}H_{18}O_6N^+$: 308.1129, found 308.1125.

4f: 44% yield, 96% *ee*. $[\alpha]_D^{25}$ = 26.3 (c = 0.79, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 242 nm, retention time: 11.22 min (major), 12.18 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 (t, J = 1.8 Hz, 1H), 7.88 (dt, J = 7.8, 1.3 Hz, 1H), 7.69 (dd, J = 8.0, 1.0 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.57 (q, 2H), 2.33 (s, 3H), 1.56 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 205.46 , 195.85 , 172.14 , 138.25 , 136.19 , 131.15 , 130.23 , 126.58 , 123.00 , 61.70 , 57.31 , 44.60 , 26.47 , 20.79 , 13.96 . IR (thin film, cm-1) 2962, 2942, 1733, 1715, 1693, 1567, 1354, 1230, 1214, 1187, 1107, 1092, 784, 680. HRMS (ESI) calcd for $C_{15}H_{17}BrO_4Na^+$: 363.0202, found 363.0201.

4g: 86% yield, 97% *ee*. $[\alpha]_D^{25}$ = -32.0 (c = 1.29, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 21.24 min (major), 27.86 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.94 (d, J = 7.0 Hz, 2H), 7.57 (t, 1H), 7.46 (t, J = 7.8 Hz, 3H), 4.17 (q, J = 7.1 Hz, 2H), 3.85 (d, J = 18.5 Hz, 1H), 3.48 (d, J = 18.5 Hz, 1H), 2.73 - 2.47 (m, 3H), 2.31 - 1.98 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 215.06 , 196.73 , 136.35 , 133.45 , 128.65 , 128.04 , 61.67 , 57.49 , 43.49 , 37.76 , 33.42 , 19.86 , 14.02 .IR data was reported previously. [3g] HRMS (ESI) calcd for $C_{16}H_{18}O_4Na^+$: 297.1097, found 297.1098.

4h: 81% yield, 91% *ee*. $[\alpha]_D^{25}$ = -30.9 (c = 3.75, $CHCl_3$). HPLC analysis: Daicel Chiralpak AD-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 259 nm, retention time: 6.76 min (major), 7.42 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.86 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 2.7 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 18.5 Hz, 1H), 3.48 (d, J = 18.4 Hz, 1H), 2.73 - 2.51 (m, 3H), 2.43 (s, 3H), 2.26 - 2.01 (m, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 215.18 , 196.34 , 170.79 , 144.32 , 133.90 , 128.16 , 61.64 , 57.49 , 43.41 , 37.79 , 33.43 , 21.68 , 19.86 , 14.02 . IR (thin film, cm-1) 2962, 2918, 2850, 1750, 1723, 1682, 1608, 1404, 1228, 1180, 1031, 1025, 810, 752, 444. HRMS (ESI) calcd for $C_{17}H_{20}O_4Na^+$: 311.1254, found 311.1252.

4i: 79% yield, 98% *ee*. $[\alpha]^D_{25}$ = -30.4 (c = 2.01, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 20:80, flow rate = 1.0 mL/min, λ = 280 nm, retention time: 38.99 min (major), 37.29 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.01 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.88 (d, J = 18.5 Hz, 1H), 3.50 (d, J = 18.4 Hz, 1H), 2.71 - 2.58 (m, 2H), 2.57 - 2.49 (m, 1H), 2.31 - 2.02 (m,3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 215.08 , 196.32 , 170.74 , 146.11 , 139.73 , 135.06 , 128.98 , 128.66 , 128.33 , 127.27 , 61.69 , 57.54 , 43.53 , 37.79 , 33.46 , 19.89 , 14.04. IR (thin film, cm-1) 2961, 2917, 2851, 1750, 1722, 1682, 1603, 1402, 1226, 1189, 1109, 990, 835, 765, 697. HRMS (ESI) calcd for $C_{22}H_{22}O_4Na^+$: 373.1410, found 373.1410.

4i: >99% yield, 98% *ee*. $[\alpha]^D_{25}$ = -35.6 (c = 2.90, $CHCl_3$). HPLC analysis: Daicel Chiralpak AD-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 242 nm, retention time: 14.34 min (major), 16.52 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.28 (d, J = 8.5 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.83 (d, J = 18.6 Hz, 1H), 3.43 (d, J = 18.6 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.58

– 2.50 (m, 2H), 2.22 – 2.15 (m, 1H), 2.14 – 2.04 (m, 2H), 1.22 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 214.55 , 195.44 , 170.37 , 150.48 , 140.73 , 129.11 , 123.88 , 61.86 , 57.52 , 43.68 , 37.62 , 33.39 , 19.83 , 13.99 . IR (thin film, cm-1) 2979, 2917, 1752, 1723, 1695, 1603, 1526, 1346, 1215, 1109, 992, 854, 747, 687. HRMS (ESI) calcd for $C_{16}H_{17}NO_6Na^+$: 342.0948, found 342.0947.

4k: 85% yield, 96% *ee*. $[\alpha]^D_{25}$ = -25.8 (c = 2.28, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 242 nm, retention time: 13.39 min (major), 15.05 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.05 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.68 (d, 1H), 7.33 (t, J = 7.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.79 (d, J = 18.6 Hz, 1H), 3.40 (d, J = 18.6 Hz, 1H), 2.90 - 2.40 (m, 3H), 2.23 - 1.99 (m, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 214.75 , 195.48 , 170.51 , 138.04 , 136.28 , 131.12 , 130.25 , 126.56 , 123.01 , 61.76 , 57.46 , 43.42 , 37.68 , 33.40 , 19.83 , 14.01 .IR (thin film, cm-1) 2962, 2917, 1751, 1723, 1690, 1567, 1351, 1214, 1108, 1094, 1031, 995, 784, 680. HRMS (ESI) calcd for $C_{16}H_{17}BrO_4Na^+$: 375.0202, found 375.0200.

4l: 61% yield, 86% *ee*. $[\alpha]^D_{25}$ = -23.1 (c = 0.76, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 268 nm, retention time: 32.36 min (major), 36.74 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.91 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.16 (d, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.79 (d, J = 18.3 Hz, 1H), 3.44 (d, J = 18.3 Hz, 1H), 2.69 - 2.56 (m, 2H), 2.53 - 2.42 (m, 1H), 2.28 - 2.03 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 215.27 , 195.20 , 170.86 , 163.74 , 130.34 , 129.47 , 113.77 , 61.62 , 57.51 , 55.50 , 43.20 , 37.79 , 33.45 , 19.86 , 14.01 . IR (thin film, cm-1) 2962, 2943, 2917, 1750, 1722, 1678, 1601, 1510, 1261, 1229, 1170, 1112, 1092, 1030, 988, 833, 752. HRMS (ESI) calcd for $C_{17}H_{20}O_5Na^+$: 327.1203, found 327.1203.

4m: 52% yield, 94% *ee*. $[\alpha]^D_{25}$ = -26.3 (c = 1.50, $CHCl_3$). HPLC analysis: Daicel Chiralpak AD-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 235 nm, retention time: 10.01 min (major), 12.21 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.04 (d, J = 8.1 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.84 (d, J = 18.6 Hz, 1H), 3.44 (d, J = 18.6 Hz, 1H), 2.80 - 2.64 (m, 1H), 2.60 - 2.54 (m, 2H), 2.26 - 1.99 (m, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 214.70 , 195.90 , 170.48 , 138.98 , 128.39 , 125.75 , 61.79 , 57.48 , 43.57 , 37.66 , 33.41 , 19.83 , 13.98 . IR (thin film, cm-1) 2962, 2943, 2917, 1751, 1723, 1693, 1512, 1410, 1324, 1168, 1130, 1111, 1066, 1015, 993, 833, 752. HRMS (ESI) calcd for $C_{17}H_{20}O_5Na^+$: 365.0971, found 365.0970.

4n: 70% yield, 98% *ee*. $[\alpha]D_{25}$ = 99.0 (c = 1.10, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 32.76 min (major), 29.17 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.94 (d, J = 6.9 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 4.23 (dd, J = 7.2, 4.6 Hz, 2H), 3.56 (d, J = 17.4 Hz, 1H), 3.38 (d, J = 17.4 Hz, 1H), 2.92 - 2.74 (m, 1H), 2.59 - 2.40 (m, 2H), 2.08 (dd, J = 6.1, 3.1 Hz, 1H), 1.89 - 1.72 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 207.29 , 196.97 , 172.03 , 136.83 , 133.10 , 128.53 , 128.05 , 61.53 , 58.93 , 44.02 , 40.55 , 36.74 , 26.83 , 22.03 , 14.06 . IR data was reported previously.[16] HRMS (ESI) calcd for $C_{17}H_{20}O_4Na^+$: 311.1254, found 311.1255.

4o: 66% yield, 99% *ee*. $[\alpha]^D_{25}$ = 32.2 (c = 1.51, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 5:95, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 32.29 min (major), 30.30 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, J = 6.9 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.85 (d, J = 17.7 Hz, 1H), 3.28 (d, J = 17.7 Hz, 1H), 3.01 - 2.83 (m, 1H), 2.69 - 2.51 (m, 1H), 2.30 (d, J = 9.6 Hz, 1H), 2.16 (d, J = 9.5 Hz, 1H), 1.86 (s, 1H), 1.80 - 1.51 (m, 4H), 1.37 - 1.27 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 209.08 , 197.28 , 171.89 , 136.88 , 133.11 , 128.54 , 128.03 , 61.66 , 61.44 , 43.92 , 41.74 , 33.07 , 30.38 , 26.16 , 24.85 , 13.98 . IR data was reported previously.[17] HRMS (ESI) calcd for $C_{18}H_{22}O_4Na^+$: 325.1410, found 325.1410.

4p: 80% yield, 97% *ee*. $[\alpha]^D_{25}$ = 97.8 (c = 1.50, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 254 nm, retention time: 69.95 min (major), 66.57 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.28 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.9 Hz, 2H), 4.26 (dd, J = 7.1, 4.3 Hz, 2H), 3.50 (d, J = 17.2 Hz, 1H), 3.30 (d, J = 17.2 Hz, 1H), 2.98 - 2.84 (m, 1H), 2.55 - 2.44 (m, 2H), 2.15 - 1.97 (m, 1H), 1.79 (d, J = 2.8 Hz, 4H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 207.25 , 195.77 , 171.79 , 150.26 , 141.48 , 129.08 , 123.78 , 61.76 , 59.63 , 44.25 , 40.52 , 37.26 , 26.98 , 21.95 , 14.06 . IR (thin film, cm-1) 2942, 2868, 1729, 1710, 1698, 1603, 1526, 1347, 1317, 1213, 1134, 1030, 854, 796, 737, 686. HRMS (ESI) calcd for $C_{17}H_{19}O_6NNa^+$: 356.1105, found 356.1103.

4q: 82% yield, 98% *ee*. $[\alpha]^D_{25}$ = 80.8 (c = 2.35, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 5:95, flow rate = 1.0 mL/min, λ = 233 nm, retention time: 18.93 min (major), 17.16 min (minor). ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 4.25 (dd, J = 7.2, 4.0 Hz, 2H), 3.52 (d, J = 17.3 Hz, 1H), 3.32 (d, J = 17.3 Hz, 1H), 2.99 - 2.80 (m, 1H), 2.57 - 2.34 (m, 2H), 2.09 (dd, J = 6.3, 3.1 Hz, 1H), 1.79 (m, 4H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 207.11 , 196.17 , 171.82 , 139.66 , 128.36 , 125.60, 126.56 , 61.63 , 59.34 , 44.09 , 40.50 , 37.03 , 26.90 , 21.97 , 14.01 . IR data wa reported previously.[3g] HRMS (ESI) calcd for $C_{18}H_{19}O_4F_3Na^+$: 379.1128, found 379.1126.

4r: >99% yield, 77% *ee*. $[\alpha]^D_{25}$ = -10.9 (c = 2.68, $CHCl_3$). HPLC analysis: Daicel Chiralpak AD-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 259 nm, retention time: 29.41 min (major), 19.32 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.32 (d, J = 8.3 Hz, 2H), 8.12 (d, J = 8.4 Hz, 2H), 4.52 (m, 1H), 4.44 (m, 1H), 3.98 (d, J = 18.8 Hz, 1H), 3.60 (d, J = 18.8 Hz, 1H), 3.15 - 2.91 (m, 1H), 2.29 (s, 4H). ^{13}C NMR (126 MHz, Chloroform-d) δ 200.56 , 194.94 , 174.88 , 150.78 , 139.99 , 129.27 , 124.08 , 66.98 , 58.24 , 44.09 , 30.72 , 25.71 . IR data was reported previously.[3g] HRMS (APCI) calcd for $C_{14}H_{14}O_6N^+$: 292.0816, found 292.0812.

4s: 58% yield, 94% *ee*. $[\alpha]^D_{25}$ = 13.7 (c = 0.76, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 242 nm, retention time: 12.41 min (major), 10.88 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (d, J = 7.0 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 3.86 - 3.55 (q, 2H), 2.60 (m, 1H), 2.49 m, 1H), 2.21 (s, 3H), 1.55 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 208.86 , 206.44 , 197.35 , 136.47 , 133.53 , 128.69 , 128.10 , 64.19 , 44.89 , 31.91 , 26.52 , 19.52 , 7.99 . IR data was reported previously.[3g] HRMS (ESI) calcd for $C_{15}H_{18}O_3Na^+$: 269.1148, found 269.1148.

4t: 69% yield, 95% *ee*. $[\alpha]D_{25}$ = 7.14 (c = 1.56, $CHCl_3$). HPLC analysis: Daicel Chiralpak OJ-H, iso-propanol/hexane = 30:70, flow rate = 1.0 mL/min, λ = 282 nm, retention time: 30.71 min (major), 27.68 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 6.9 Hz, 2H), 7.47 (t, J = 7.5 Hz, 2H), 7.41 (t, 1H), 3.73 (q, 2H), 2.62 (dd, J = 18.3, 7.2 Hz, 1H), 2.52 (dd, J = 18.3, 7.1 Hz, 1H), 2.22 (s, 3H), 1.57 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 208.90 , 206.48 , 196.95 , 146.22 , 139.70 , 135.17 , 128.99 , 128.73 , 128.36 , 127.31 , 127.28 , 64.25 , 44.91 , 31.94 , 26.54 , 19.56 , 8.02 . IR (thin film, cm-1) 2981, 2938, 2923, 2853, 1698, 1678, 1603, 1449, 1400, 1351, 1224, 1169, 958, 834, 765, 721, 691. HRMS (ESI) calcd for $C_{21}H_{22}O_3Na^+$: 345.1461, found 345.1460.

4u: 52% yield, 97% *ee*. $[\alpha]^D_{25}$ = -3.4 (c = 0.55, $CHCl_3$). HPLC analysis: Daicel Chiralpak OD-H, iso-propanol/hexane = 20:80, flow rate = 1.0 mL/min, λ = 240 nm, retention time: 9.67 min (major), 10.70 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 (d, J = 7.0 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz,

2H), 3.70 (q, J = 4.5 Hz, 2H), 2.44 (m, 1H), 2.38 - 2.26 (m, 1H), 2.20 (s, 3H), 1.53 (s, 3H), 0.89 (dd, J = 6.7, 2.7 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 207.31 , 206.31 , 197.27 , 136.53 , 133.52 , 128.69 , 128.10 , 64.68 , 47.14 , 44.65 , 26.61 , 23.67 , 22.40 , 22.37 , 19.29 . IR data was reported previously.[3g] HRMS (ESI) calcd for $C_{17}H_{22}O_3Na^+$: 297.1461, found 297.1460.

4v: 76% yield, 90% *ee*. $[\alpha]^D_{25}$ = 4.7 (c = 1.67, $CHCl_3$). HPLC analysis: Daicel Chiralpak AD-H, iso-propanol/hexane = 10:90, flow rate = 1.0 mL/min, λ = 260 nm, retention time: 18.48 min (major), 17.46 min (minor). ^{1}H NMR (500 MHz, Chloroform-d) δ 8.30 (d, J = 8.9 Hz, 2H), 8.11 (d, J = 8.9 Hz, 2H), 3.67 (q, J = 3.0 Hz, 2H), 2.46 (dd, J = 17.8, 6.7 Hz, 1H), 2.34 (dd, J = 17.8, 6.7 Hz, 1H), 2.23 (s, 3H), 1.57 (s, 3H), 0.89 (dd, J = 6.7, 3.2 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-d) δ 207.07 , 206.05 , 195.97 , 150.50 , 140.93 , 129.16 , 123.91 , 64.64 , 47.30 , 45.04 , 26.68 , 23.70 , 22.36 , 22.40 , 19.36 . IR (thin film, cm-1) 2960, 2920, 2872, 1697, 1604, 1526, 1468, 1406, 1344, 1319, 1214, 1034, 1010, 853. HRMS (ESI) calcd for $C_{17}H_{21}O_5NNa^+$: 342.1312, found 342.1308.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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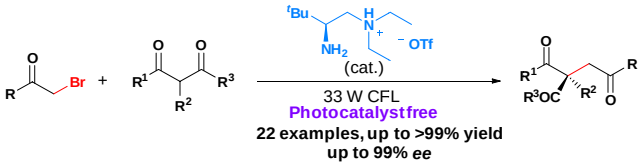

Enantioselective α-photoalkylation of β-ketocarbonyls without any external photosensitizer was described, which provided convenient constructions of all-carbon quaternary stereocenters by a chiral primary amine catalyst.

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