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Functionalized Chiral Ionic Liquid Catalyzed Asymmetric S_N1 α-Alkylation of Ketones and Aldehydes

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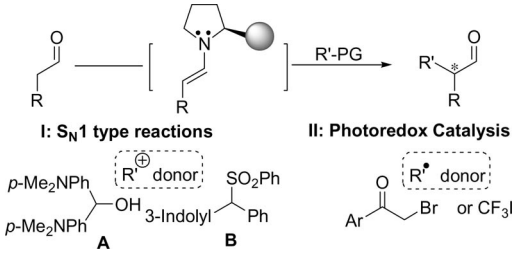
Pyrrolidine-derived functionalized chiral ionic liquids (FCILs) have been found to catalyze asymmetric S_N1 α-alkylations of ketones and aldehydes with up to 99 % yield, >99:1 *dr* and 87 % *ee*. The FCIL catalysts enable S_N1 α-alkylations of cyclic ketones, particularly of 3- and 4-substituted cyclohexanones with excellent diastereoselectivity and good enantioselectivity, featuring unprecedented desymmetrization and kinetic resolution processes for these types of asymmetric reaction. Full details of this study as well as the proposed enamine transition-state are presented.

1. Introduction

Asymmetric α-alkylation of carbonyl compounds has long been recognized as a powerful tool in modern organic synthetic chemistry. Great efforts have been made to develop chiral auxiliaries based α-alkylation reactions in the past half century and a variety of successful examples have been reported.[1–3] Despite these advances, catalytic asymmetric α-alkylation reactions are still rare. Many catalytic methodologies have been attempted for this purpose, and most of the successes have been achieved with chiral phase-transfer catalysis (PTC).[4] Currently, the substrates of chiral PTC are limited to stabilized enolates such as glycine derivatives, and direct nucleophilic α-alkylation of aldehydes and ketones could not be realized through this approach. Ever since the renaissance of organocatalysis in 2000, enamine-based catalysis has become an attractive strategy for α-alkylation reactions, with their origins deeply rooted in classical enamine-alkylation chemistry.[1a,5]

However, it was not until 2004 that Vignola and List reported the first catalytic intramolecular nucleophilic α-alkylation of aldehydes through enamine activation.[6] Subsequently, several cascade reactions involving intramolecular α-alkylation of aldehydes as the key step were also reported.[7] However, intermolecular asymmetric α-alkylation of carbonyl compounds is still a challenging task in enamine catalysis due to depletion of catalytic activity through N-alkylation of the aminocatalysts and various competing pathways. More recently, Melchiorre and Cozzi have independently reported S_N1-type α-alkylation of aldehydes through enamine catalysis by taking advantage of stable carbocations generated in situ from alkyl donors **A** and **B** (Scheme 1, I).[8,9] In another notable advance, MacMillan and coworkers developed an enamine-based photoredox catalysis, wherein the enamine was intercepted with a photo-generated, stabilized alkyl radical (Scheme 1, II).[10] In this context, the direct asymmetric intermolecular α-alkylation of ketones remains an elusive goal. Only chiral transition-metal catalysts have been reported to promote asymmetric direct α-alkylation of ketones, but these reactions were limited to allylation or vinylation reactions,[11] no organocatalytic process for this transformation has been achieved to date.



Scheme 1. Organocatalytic strategies for asymmetric intermolecular alkylation of aldehydes.

The past decade has witnessed the burgeoning development of functionalized chiral ionic liquids (FCILs) in organic synthesis and catalysis,[12] especially in their application as asymmetric catalysts.[13,14] In our continuing efforts to explore this type of catalysis,[14a–14c,14k] we have been seeking new reactions by taking advantage of the intrinsic properties of ionic liquids. Bearing in mind the highly polar and ionic nature of ionic liquids, it was envisaged that

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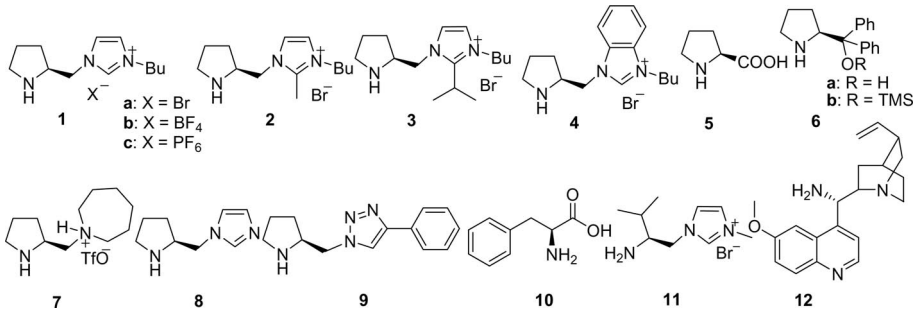
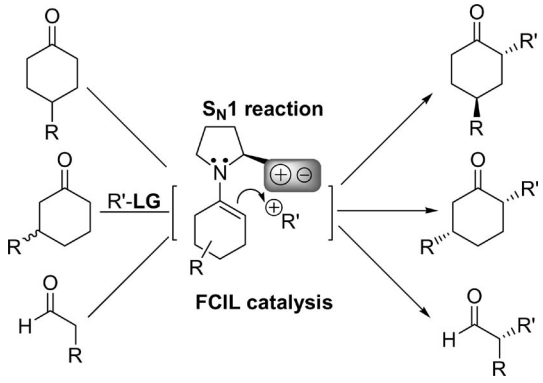


Figure 1. Catalysts tested in this study.

FCILs might provide a favorable catalytic sphere for direct α-alkylation of ketones and aldehydes in which ionic intermediates or transition-states such as carbocations are involved (Scheme 2). We found that FCILs such as **1**–**4** (Figure 1) could indeed catalyze α-alkylation reactions of cyclic ketones[15] and, furthermore, this reaction could be applied to the alkylation of 3- and 4-substituted cyclohexanones and aldehydes. Herein, we report details of our studies on this α-alkylation reaction.



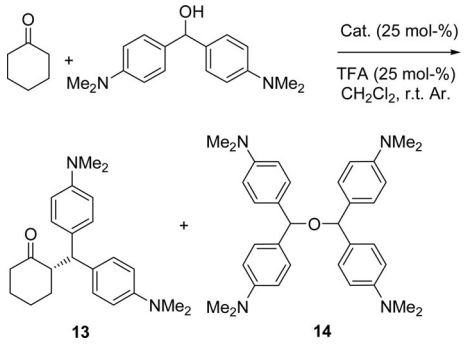
Scheme 2. FCIL-catalyzed asymmetric intermolecular α-alkylation of ketones and aldehydes (this work).

2. Results and Discussion

2.1 Screening of Conditions

The 4,4′-bis(dimethylamino)diphenylmethane carbocation, which has been shown to be very stable at room temperature,[16] could be generated in situ from bis(4,4′-dimethylaminophenyl)methanol under acidic conditions. Thus, direct α-alkylation of cyclohexanone with this stable carbocation was selected as the model reaction. Firstly, various enamine-based organocatalysts were tested; the results are summarized in Table 1. To our delight, the secondary amine-based FCIL catalysts showed good catalytic activity in this reaction. For instance, with FCIL **1a**, the reaction proceeded smoothly to afford the desired product with 65% yield and 72% *ee* in 48 hours, together with a minor amount of byproduct **14** (Table 1, entry 1). Changing the bromide anion to larger anions such as BF_4^- or PF_6^- dramatically decreased the enantioselectivity, although in these cases the reaction gave solely the alkylation products (Table 1, entries 2 and 3). Use of FCILs bearing bulky groups at the imidazolium ring, such as **2** and **3**, did not give superior results compared to those obtained with FCIL **1a** (Table 1, entries 4 and 6). Reducing the reaction tem-

Table 1. Screening of catalysts.[a]



Entry	Catalyst	Time [h]	Yield of **13** [%][b]	Yield of **14** [%][b]	*ee* of **13** [%][c]
1	**1a**	48	65	13	72
2	**1b**	48	64	–	54
3	**1c**	48	80	–	38
4	**2**	48	48	19	69
5[e]	**2**	12	24	60	74
6	**3**	48	62	8	64
7[e]	**3**	12	14	58	62
8	**4**	*48*	*51*	*27*	*79*
9	**5**	12	70	–	16
10	**6a**	20	–	77	–
11	**6b**	20	–	99	–
12	**7**	7	83	–	57
13	**8**	40	72	23	66
14	**9**	12	88	–	66
15	**10**	10	51	–	16
16	**11**	48	40	–	23
17	**12**	20	40	n.d.[d]	40

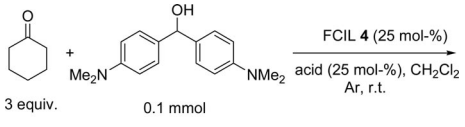
[a] Reaction conditions (0.1 mmol scale): ketone (3 equiv.), catalyst (25 mol-%), r.t., under argon. [b] Isolated as a mixture of **13** and **14**, the yield was calculated based on the ratio of **13**/**14**, determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC analysis. [d] Combined yield of **13** and **14**, the ratio was not determined. [e] Reactions conducted at 4 °C.

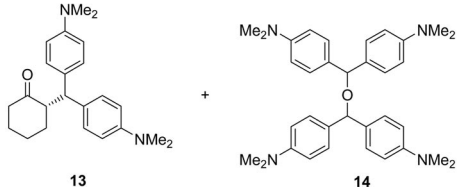
perature led to slightly increased enantioselectivity, but at the expense of a significant decrease in activity and an increase in the formation of byproduct **14** (Table 1, entries 5 and 7). To our delight, the benzoimidazolium cation based FCIL **4** was found to greatly improve the enantioselectivity (79% *ee*, Table 1, entry 8). Typical secondary amine catalysts such as **5**–**7** and **9**, FCIL precursor **8**, as well as some primary amine catalysts **10**–**12**, were also examined in this reaction. Amino acids **5** and **10** gave only very low enantioselectivities in the presence of trifluoroacetic acid (TFA) (Table 1, entries 9 and 15). Surprisingly, catalysts **6a** and **6b** mainly produced the byproduct **14**, even though these privileged skeletons have been shown to be very effective in many other enamine-based reactions. Catalysts **7**–**9** gave comparable results to those obtained with FCIL **1a**, although with slightly lower enantioselectivity (Table 1, entries 12–14), whereas other primary amines gave both low yields and *ee* values (Table 1, entries 16 and 17). Overall, FCIL **4** was identified as the optimal catalyst in terms of both activity and stereoselectivity.

With FCIL **4** as the optimal catalyst, the reaction was further optimized by screening a range of acidic additives with the aim of further improving the catalytic activity and decreasing the amount of byproduct formation. The acidic additive was found to be essential because no reaction occurred without the acid (Table 2, entry 1). Both strong acids, such as TfOH and $HClO_4$, and weak acids such as HOAc, PhCOOH, led to low yields and *ee* (Table 2, entries 2–5). The use of sulfonic acids such as *p*-toluenesulfonic acid and camphorsulfonic acid gave good enantioselectivity, but the isolated product contained significant amounts of byproduct **14** (Table 2, entries 6 and 7). Improved performance was observed with substituted benzoic acids as additives (Table 2 entries 9, 10, 12, and 13). Among the benzoic acids screened, phthalic acid was found to give optimal yield and *ee* values. Encouragingly, the formation of byproduct **14** was completely inhibited when the acid loading was increased to 37.5 mol-%, while the enantioselectivity was maintained (Table 2, entry 14). Further increasing the loading of phthalic acid slightly decreased both the yield and selectivity (Table 2, entries 15 and 16).

The effect of solvent was next explored in order to further improve the activity of FCIL **4**. Except for 1,2-dichloroethane (Table 3, entry 8), inferior results were obtained in solvents other than CH_2Cl_2. For example, reactions in non-polar solvents such as *n*-hexane, Et_2O and toluene gave mainly the byproduct **14** (Table 3, entries 1–3), and similar results were obtained in polar solvents such as tetrahydrofuran (THF), CH_3CN and *t*BuOH (Table 3, en-

Table 2. Screening of acid additive.[a]

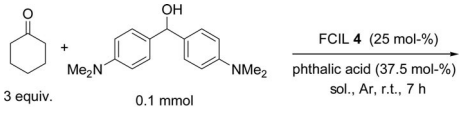


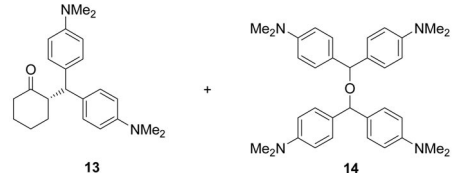


Entry	Acid	Time [h]	Yield of **13** [%][b]	Yield of **14** [%][b]	*ee* of **13** [%][c]
1	–	–	n. r.[d]	–	–
2	TfOH	48	45	n. d.[e]	31
3	$HClO_4$	48	30	n. d.[e]	64
4	CH_3COOH	48	10	n. d.[e]	–
5	PhCOOH	48	50	n. d.[e]	73
6	PTSA	48	60	n. d.[e]	82
7	CSA	48	30	n. d.[e]	83
8	TFA	48	51	27	79
9	*o*-OH-PhCOOH	48	44	40	85
10	*m*-NO_2-PhCOOH	48	45	39	84
11	terephthalic acid	48	<10	–	–
12	isophthalic acid	48	<40	n.d.[e]	86
13	phthalic acid	48	80	3	82
14[f]	*phthalic acid*	*20*	*86*	–	*82*
15[g]	phthalic acid	20	77	–	81
16[h]	phthalic acid	20	60	–	78

[a] Reaction conditions (0.1 mmol scale): ketone (3 equiv.), catalyst (25 mol-%), r.t., under argon. [b] Isolated as a mixture of **13** and **14**, the yield was calculated based on the ratio of **13**/**14**, determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis using a chiral OD-H column. [d] No reaction. [e] Combined yield of **13** and **14**, the ratio was not determined. [f] 37.5 mol-% acid was added. [g] 50 mol-% acid was added. [h] 100 mol-% acid was added.

Table 3. Solvent screening.[a]





Entry	Solvent	Yield of **13** [%][b]	Yield of **14** [%][b]	*ee* of **13** [%][c]
1	*n*-hexane	17	46	69
2	Et_2O	14	62	71
3	toluene	9	31	75
4	THF	51	32	82
5	CH_3CN	17	19	77
6	CH_2Cl_2	70	–	82
7	$CHCl_3$	60	4	80
8	*$ClCH_2CH_2Cl$*	*80*	–	*82*
9[d]	$ClCH_2CH_2Cl$	trace	n.d.[e]	–
10	*t*BuOH	23	38	80
11	H_2O	n. r.[f]	–	–
12	neat	66	15	74

[a] Reaction conditions (0.1 mmol scale): ketone (3 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), r.t., under argon. [b] Isolated as a mixture of **13** and **14**, the yield was calculated based on the ratio of **13**/**14**, determined by ^1H NMR spectroscopy. [c] Determined by HPLC analysis. [d] 4 Å molecular sieves (20 mg) was used. [e] Not determined. [f] No reaction.

tries 4, 5, 10). Interestingly, no reaction was observed in water (Table 3, entry 11). The reaction also occurred with no added solvent, but gave low yield and enantioselectivity (Table 3, entry 12). To our delight, the reaction was considerably accelerated in 1,2-dichloroethane without any formation of byproduct **14** (Table 3, entry 8). Under these conditions, the reaction was complete in seven hours with 80% yield and 82% *ee*.

2.2 Substrate Scope

Under the optimal conditions, the scope of the reaction was next explored with various donors including: acyclic ketones, cyclic ketones, 4-substituted cyclohexanones, 3-substituted cyclohexanones, as well as aldehydes. Other acceptors such as **A1b**–**A3** were also examined (Figure 2). The results were summarized in Tables 4, 5, 6, 7, and 8.

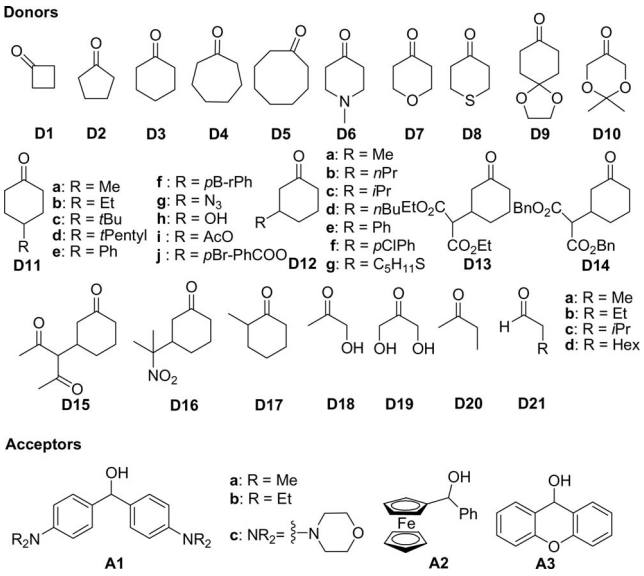
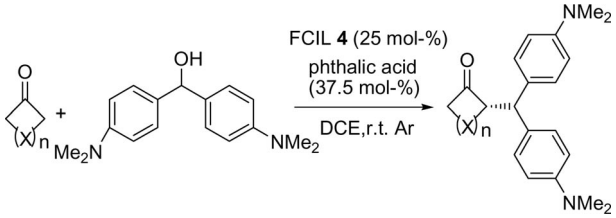


Figure 2. Donors and acceptors tested in this study.

Firstly, direct α-alkylation of cyclic ketones with varied ring sizes with acceptor **A1a** was tested; the results are listed in Table 4. As shown, cyclic ketones reacted quite differently. Whereas the reactions of cyclobutanone **D1** and cyclohexanone **D3** worked well (Table 4, entries 1 and 3), surprisingly, cyclic ketones with five-, seven- and eight-membered ring sizes showed no activity in this reaction (**D2**, **D4**, and **D5**; Table 4, entries 2, 4, and 5). The reason for this inertness is still unclear. Other cyclohexanones such as 4-oxa- and 4-thio-cyclohexanone (**D7** and **D8**; Table 4, entries 7 and 8) gave the desired products in moderate to excellent yield with high *ee* values. 4-Azacyclohexanone (**D6**) and 1,4-cyclohexanedione monoketal (**D9**) also produced the desired products with reasonable yields but with low enantioselectivity (Table 4, entries 6 and 9). Under the optimal conditions, donor **D10** gave no desired product due to decomposition (Table 4, entry 10).

Bearing in mind our previous successes with desymmetrization reactions,[14c,17] we next explored the desymmetrization of 4-substituted cyclohexanones using the asymmetric α-alkylation reaction. To our delight, the reactions worked extremely well with these substrates, and led to an unprecedented desymmetrization process. Most of the substrates could gave the desired product in excellent yields (up to 99%) with greater than 99:1 diastereoselectivity and more than 80% enantioselectivity; in the cases of **D11g**, **D11i**, and **D11j**, a slight decrease in diastereoselectivity was found, but good enantioselectivity was still obtained (Table 5, entries 7, 9, and 10).

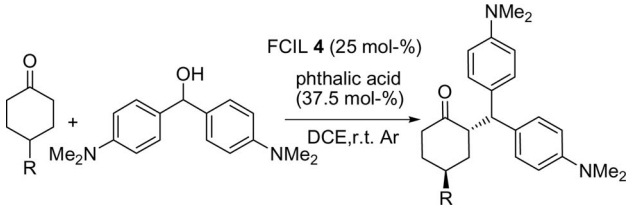
Table 4. Direct α-alkylation of cyclic ketones **D1**–**D10** with **A1a**.[a]



Entry	Donor	Time [h]	Yield [%][b]	*ee* [%][c]
1	**D1**	7	69 (**15**)	44
2	**D2**	7	n. r.[d]	–
3	**D3**	7	80 (**13**)	82
4	**D4**	7	n. r.[d]	–
5	**D5**	7	n. r.[d]	–
6	**D6**	18	60 (**16**)	32
7	**D7**	7	93 (**17**)	80
8	**D8**	18	82 (**18**)	77
9	**D9**	18	66 (**19**)	57
10	**D10**	18	dec.	–

[a] Reaction conditions (0.1 mmol scale): ketone (3 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), DCE (0.2 mL), r.t., under argon. [b] Isolated yield. [c] Determined by HPLC analysis. [d] n. r.: no reaction.

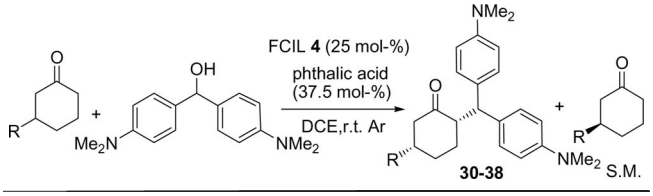
Table 5. Direct α-alkylation of 4-substituted cyclohexanones with **A1a**.[a]



Entry	Donor	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**D11a**	12	94 (**20**)	>99:1	85
2	**D11b**	12	82 (**21**)	>99:1	80
3	**D11c**	12	89 (**22**)	>99:1	81
4	**D11d**	12	90 (**23**)	>99:1	87
5	**D11e**	12	89 (**24**)	>99:1	82
6	**D11f**	18	99 (**25**)	>99:1	80
7	**D11g**	12	99 (**26**)	90:10	85
8	**D11h**	12	99 (**27**)	>99:1	72
9	**D11i**	18	98 (**28**)	84:16	77
10	**D11j**	24	86 (**29**)	87:13	78

[a] Reaction conditions (0.1 mmol scale): ketone (3 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), DCE (0.2 mL), r.t., under argon. [b] Isolated yield. [c] Determined by ^{1}H NMR or HPLC analysis. [d] Determined by HPLC analysis.

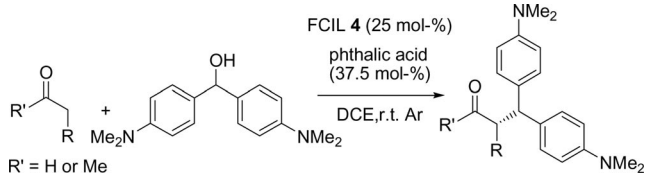
Table 6. Direct α-alkylation of 3-substituted cyclohexanones with **A1a**.[a]



Entry	Donor	Time [h]	Yield [%][b]	*dr*[c]	S.M. [%][d]	*ee* [%][e]
1	**D12a**	72	56 (**30**)	>99:1	–	80
2[f]	**D12a**	48	80 (**30**)	>99:1	–	80
3	**D12b**	72	57 (**31**)	>99:1	7	FD[g]
4[f]	**D12b**	48	66 (**31**)	98:2	–	FD[g]
5	**D12c**	72	57 (**32**)	>99:1	21	76
6[f]	**D12c**	48	51 (**32**)	>99:1	–	74
7	**D12d**	72	54 (**33**)	>99:1	37	74
8[f]	**D12d**	48	67 (**33**)	>99:1	–	75
9	**D12e**	72	77 (**34**)	>99:1	32	79
10	**D12f**	72	67 (**35**)	>99:1	24 (26% *ee*)	76
11	**D12g**	72	n. r.[h]	–	–	–
12	**D13**	72	66 (**36**)	91:9	40 (18% *ee*)	69
13[i]	**D13**	80	77 (**36**)	91:9	–	71
14	**D14**	72	57 (**37**)	90:10	22	FD[g]
15	**D15**	72	50 (**38**)	99:1	–	59
16	**D16**	72	75 (**39**)	99:1	23	84
17	**D17**	72	n. r.[h]	–	–	–

[a] Reaction conditions (0.1 mmol scale): ketone (2 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), DCE (0.2 mL), r.t., under argon. [b] Isolated yield. [c] Determined by ^{1}H NMR or HPLC analysis. [d] Starting material. [e] Determined by HPLC analysis. [f] Ketone (4 equiv.) was used. [g] Not determined. [h] No reaction. [i] Reaction conditions (0.5 mmol scale): Ketone (2 equiv.), catalyst (10 mol-%), phthalic acid (15 mol-%), DCE (2 mL), r.t., under argon.

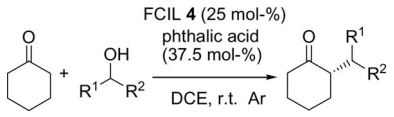
Table 7. Direct α-alkylation of acyclic ketones and aldehydes with **A1a**.[a]



Entry	Donor	Time [h]	Yield [%][b]	*ee* [%][c]
1	**D18**	24	99 (**40**)	34
2	**D19**	24	n. r.	–
3	**D20**	24	n. r.	–
4[d]	**D21a**	22	>99(**41**)	50
5[d]	**D21b**	22	>99(**42**)	33
6[e]	**D21c**	7	88 (**43**)	59
7[d]	**D21c**	7	90 (**43**)	66
8[d]	**D21d**	22	>99 (**44**)	48

[a] Reaction conditions (0.1 mmol scale): ketones or aldehydes (3 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), DCE (0.2 mL), r.t., under argon. [b] Isolated yield. [c] Determined by HPLC analysis. [d] FCIL **2** (25 mol-%) was used as catalyst, TFA (25 mol-%) was used as acidic additive, CH_2Cl_2 (0.2 mL) was used as solvent. [e] FCIL **4** (25 mol-%) was used as catalyst, TFA (25 mol-%) was used as acidic additive, CH_2Cl_2 (0.2 mL) was used as solvent.

Table 8. Direct α-alkylation of cyclohexanone with **A1a**–**A3**.[a]



Entry	Acceptor	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**A1a**	7	80 (**15**)	–	82
2	**A1b**	12	57 (**45**)	–	71
3	**A1c**	12	56 (**46**)	–	68
4	**A2**	40	43 (**47**)	2:1	8 (major), 13 (minor)
5	**A3**	12	trace	–	–

[a] Reaction conditions (0.1 mmol scale): ketones or aldehydes (3 equiv.), catalyst (25 mol-%), phthalic acid (37.5 mol-%), DCE (0.2 mL), r.t., under argon. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis.

With these results in hand, we were promoted to apply the reaction conditions to 2- and 3-substituted cyclohexanones. In these reactions, kinetic resolution of 2- or 3-substituted cyclohexanones would also occur. The results are summarized in Table 6. Again, the reaction with 3-substituted cyclohexanones occurred readily to afford regio- and diastereoselectively the desired α-alkylated products. Although minor amounts of byproduct **14** were observed, no unwanted regioisomers were detected and, in most cases, the desired products were isolated with up to >99:1 *dr* and 84% *ee*. The enantioselectivity of the recovered 3-substituted cyclohexanones were also determined to examine the ability of FCIL catalysis to facilitate kinetic resolution. Unfortunately, only low *ee* values were obtained (24% and 18%; Table 6, entries 10 and 12). Because the reaction proceeded very sluggishly with limiting loading of ketone donors, the kinetic resolution properties were not pursued further. To improve the yields, four equivalents of donor loading were then tested (Table 6, entries 2, 4, 6, and 8). Under these conditions, slightly increased isolated yields were obtained in most cases, and comparable diastereo- and enantioselectivities were observed. When a larger scale reaction (0.5 mmol) was conducted using 10 mol-% catalyst and 15 mol-% acidic additive (Table 6, entry 13), the reaction was complete in 80 hours with 77% yield and 71% *ee*. It should be noted that when 3-pentylthiocyclohexanone was used as the donor, no desired product could be isolated (Table 6, entry 11). When 2-methylcyclohexanone was submitted to the reaction conditions no reaction occurred (Table 6, entry 17).

Acyclic ketones and aldehydes were also examined under the conditions described above. However, among all the acyclic ketones tested, only hydroxyacetone gave the desired product (34% *ee*; Table 7, entry 1), other ketones showed completely no activity (Table 7, entries 2 and 3). Initial trials with aldehyde **D21c** in this reaction gave 88% isolated yield in seven hours, but only moderate enantioselectivity could be obtained (59% *ee*; Table 7, entry 6). Screening of other FCIL catalysts led to only a slight increase in both

yield and enantioselectivity when FCIL **2** was used as a catalyst with TFA as an additive (Table 7, entry 7). Other aldehydes also gave excellent isolated yields with low to moderate enantioselectivity.

Other accepters such as **A1b**–**A3** were also tested in the reaction; the results are summarized in Table 8. However, in all cases, both the yield and enantioselectivity were decreased. According to Mayr's electrophilic scale (*E*), alcohols with more negative *E* values performed relatively better and gave higher yields and *ee* values (e.g., *E* = –7.02 for the cation from **A1a**, *E* = –5.53 for the cation from **A1c**, Table 8, entries 1–3).[16b] These results indicated that the stability of the carbocation formed in situ was essential for the reaction. Following this trend, alcohols that form unstable carbocations (with *E* values close to zero), such as **A2** (*E* = –2.64) and **A3** (*E* = –0.99),[16d] are not suitable substrates for this alkylation reaction and demonstrate very low reactivities (Table 8, entries 4 and 5). Similar reactivity trends have also been reported by Cozzi.[9a]

Taking the reaction of **D11d** and **A1a** as a model, the recyclability of the FCIL catalyst was tested under the optimal conditions. It was found that the catalyst could be reused at least four times with similar activity, diastereoselectivity, and enantioselectivity. Diminishing activity and selectivity were found in the fourth recycle, but good yields and *ee* were maintained throughout (Figure 3).

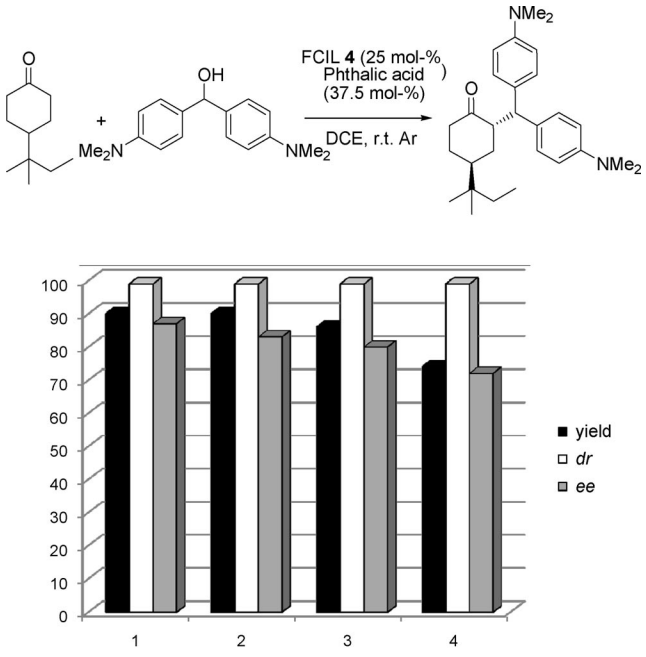


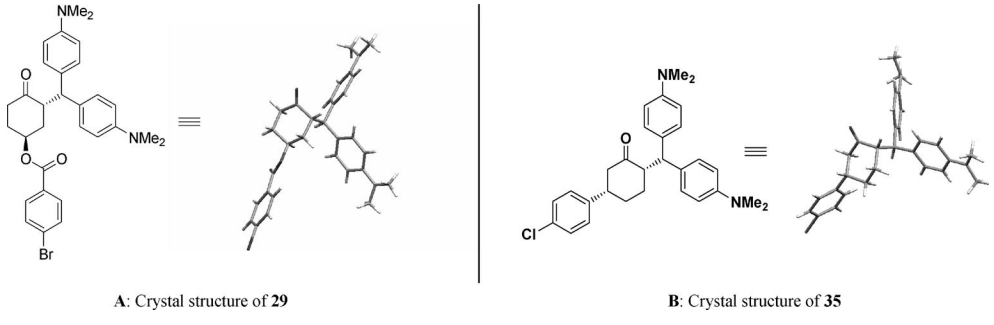
Figure 3. Recycling and reuse of FCIL **4**.

2.3 Proposed Mechanism

The relative and absolute configurations of the α-alkylated products were determined by X-ray crystallographic analyses. Accordingly, the crystal structure of compound **29** − an α-alkylated product derived from 4-substituted cyclohexanone − shows a 2,4-*trans*-disubstituted structure with (2*S*,4*S*) configuration (Figure 4, **A**),[18] whereas the crystal structure of compound **35** − an α-alkylated product derived from 3-substituted cyclohexanone − features a 2,5-*cis*-disubstituted structure with (2*S*,5*S*) configuration (Figure 4, **B**).[19] These stereochemical outcomes can be rationalized by invoking classical half-chair enamine transition-states; the favored enamine transition-states **II** and **VI** can thus be formulated through typical conformational analysis for 4- and 3-substituted cyclohexanones, respectively (Scheme 3).[20] In this transition state, the ionic liquid moiety would effectively shield the *Si*-face of the enamine by steric repulsion as well as by electrostatic interaction. The reaction occurs through axial *Re*-face attack of the carbocation to minimize the $A^{(1,3)}$ strain arising from the bulky nature of the carbocation. The different relative configurations of the α-alkylated products of 4- and 3-substituted cyclohexanones can be explained by assuming late transition-states in these reactions, wherein the formation of two axial substitutes (**I**→**III**, **V**→**VII** for 4- and 3-substituted cyclohexanones, respectively) are disfavored.

3. Conclusion

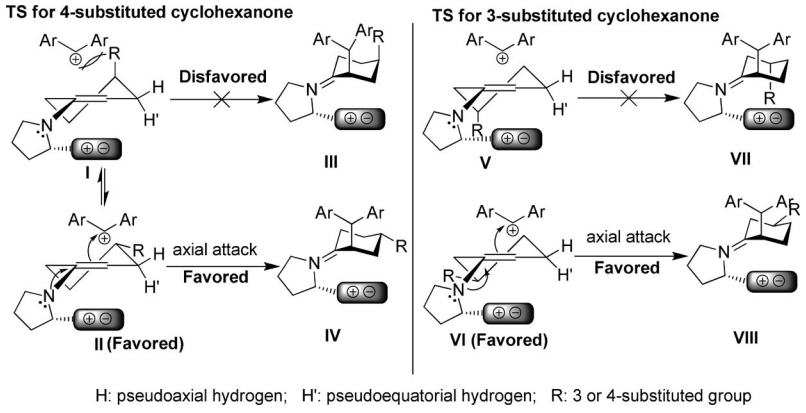
We have presented a full account of our investigations into FCIL-catalyzed asymmetric S_N1-type α-alkylation of carbonyl compounds. Notably, the current catalytic system enables asymmetric desymmetrization of 4-substituted cyclohexanones to afford 2,4-*trans*-substituted products with up to 99% yield, greater than 99:1 *dr* and 87% *ee*. Similarly, the reactions of 3-substituted cyclohexanones give 2,5-*cis*-substituted products with up to 80% yield, more than 99:1 *dr* and 84% *ee*. The limitations and scope of the reaction



A: Crystal structure of **29**

B: Crystal structure of **35**

Figure 4. Crystal structures of **29** and **35**.



Scheme 3. Proposed transition states.

were further demonstrated with a range of donors, such as acyclic ketones and aldehydes, and different carbocation acceptors. Half-chair enmaine transition-states were proposed to account for the observed stereoselectivity.

Experimental Section

General Information: Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker-DPX 300 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane or with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br. = broad. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m) or broad (br). Mass spectra were obtained with an electron impact ionization (EI) mass spectrometer or with an electrospray ionization (ESI) mass spectrometer. IR spectra were obtained with a Jasco FT/IR-480 Plus instrument. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin–Elmer 341 digital polarimeter and are reported as follows: $[a]_D^{20}$ (c in g per 100 mL of solvent). HPLC analysis was performed on a Varian Prostar instrument using ChiralPak AD-H, OD-H or AS-H columns purchased from Daicel Chemical Industries, Ltd. Alcohols **A1a**, **A1b**, **A1c** and **A3** were obtained by reduction of the corresponding ketones, alcohol **A2** was prepared from commercially available aldehyde by the addition of phenylmagnesium bromide.

General Procedure for S_N1 Alkylation of Ketones: Catalyst **4** (8.5 mg, 25 mol-%) and phthalic acid (6.3 mg, 37.5 mol-%) were dissolved in 1,2-dichloroethane (0.2 mL) in a glass vial. To this solution, bis(4-dimethylaminophenyl)methanol (27 mg, 0.1 mmol) and cyclohexanone (31 μL, 3 equiv.) were then added. The reaction mixture was stirred at r.t. under argon for 7 h, then the solvent was removed under reduced pressure and the residue was extracted with diethyl ether (4 × 5 mL). The combined organic layers were concentrated and loaded directly onto a silica gel column for purification. The desired product **13** was isolated as a white solid (28 mg, 80% yield) in 82% *ee* [HPLC analysis on a chiralpak AD-H column; λ = 254 nm; eluent *i*PrOH/*n*-hexane (15:85, *v*/*v*); flow rate = 0.7 mL/min; t_R = 9.48 min (minor), 10.23 min (major)]. The recovered catalyst was reused directly in the next run after removal of the residual solvent.

Products **10**–**29** have been previously reported.[14] Products **41**–**44** are also known compounds.[8]

Characterization Data for New Compounds

Compound 30: Yield 29 mg, 80%; >99:1 *dr*; white solid. $[a]_D^{20}$ = –70 (80% *ee*; *c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.54 Hz, 3 H, CH_3), 1.60–1.78 (m, 4 H, 2 × CH_2), 1.93–2.00 (m, 1 H, CH), 2.18–2.22 (m, 2 H, CH_2), 2.85 [s, 6 H, $N(CH_3)_2$], 2.88 [s, 6 H, $N(CH_3)_2$], 3.14–3.20 (m, 1 H, CH), 4.14 (d, *J* = 11.86 Hz, 1 H, Ph_2CH), 6.60–6.67 (m, 4 H, 4 × ArH), 7.10–7.16 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 29.2, 35.9, 40.6, 40.7, 48.0, 49.7, 54.8, 112.8, 112.9, 128.4, 130.8, 131.4, 149.1, 149.2, 214.1 ppm. IR (KBr): $\tilde{\nu}$ = 2952, 2939, 2922, 2868, 2849, 2796, 1702, 1614, 1563, 1519, 1479, 1458, 1443, 1349, 803 cm^{-1}. HRMS (EI): calcd. for $C_{24}H_{32}N_2O$ [M] 364.2515; found 364.2518. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 1.0 mL/min; t_R = 10.41 min (minor), 12.20 min (major).

Compound 31: Yield 26 mg, 66%; 98:2 *dr*; white solid. $[a]_D^{20}$ = –87 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.30 Hz, 3 H, CH_3), 1.26–1.39 (m, 4 H, 2 × CH_2), 1.60–1.71 (m, 3 H, CH_2 + CH), 1.77–1.84 (m, 2 H, CH_2), 2.22 (d, *J* = 7.95 Hz, 2 H, CH_2), 2.86 [s, 6 H, $N(CH_3)_2$], 2.89 [s, 6 H, $N(CH_3)_2$], 3.17–3.22 (m, 1 H, CH), 4.15 (d, *J* = 11.95 Hz, 1 H, Ph_2CH), 6.60–6.67 (m, 4 H, 4 × ArH), 7.11–7.17 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.9, 27.1, 29.2, 38.8, 40.5, 40.6, 40.7, 46.1, 49.7, 55.2, 112.8, 112.9, 128.4, 130.9, 131.4, 149.1, 149.2, 214.2 ppm. IR (KBr): $\tilde{\nu}$ = 2924, 2861, 2803, 1701, 1614, 1521, 1448, 1350, 806 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{36}N_2O$ [M] 392.2828; found 392.2831. We failed to determine the *ee*.

Compound 32: Yield 22 mg, 57%; >99:1 *dr*; white solid. $[a]_D^{20}$ = –60 (76% *ee*; *c* = 0.125, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90–0.94 (m, 6 H, 2 × CH_3), 1.58–1.74 (m, 5 H, 2 × CH_2 + CH), 1.79–1.85 (m, 1 H, CH), 2.15–2.19 [m, 1 H, C(H)H], 2.26–2.33 [m, 1 H, C(H)H], 2.86 [s, 6 H, $N(CH_3)_2$], 2.89 [s, 6 H, $N(CH_3)_2$], 3.17–3.22 (m, 1 H, CH), 4.13 (d, *J* = 12.06 Hz, 1 H, Ph_2CH), 6.60–6.68 (m, 4 H, 4 × ArH), 7.13–7.18 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 19.8, 23.7, 29.1, 32.8, 40.6, 40.7, 43.0, 47.2, 49.8, 55.1, 112.8, 113.0, 128.4, 128.5, 130.6, 131.3, 149.1, 149.2, 215.1 ppm. IR (KBr): $\tilde{\nu}$ = 2932, 2864, 2799, 1704, 1613, 1520, 1474, 1448, 1350, 807 cm^{-1}. HRMS (EI): calcd. for $C_{26}H_{36}N_2O$ [M] 392.2828; found 392.2833. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 0.5 mL/min; t_R = 16.89 min (minor), 18.18 min (major).

Compound 33: Yield 27 mg, 67%; >99:1 *dr*; white solid. $[\alpha]_D^{20}$ = –78 (75% *ee*; *c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.65 Hz, 3 H, CH_3), 1.27–1.40 (m, 6 H, 3 × CH_2), 1.60–1.70 (m, 3 H, CH_2 + CH), 1.76–1.84 (m, 2 H, CH_2), 2.23 (d, *J* = 7.95 Hz, 2 H, CH_2), 2.86 [s, 6 H, $N(CH_3)_2$], 2.89 [s, 6 H, $N(CH_3)_2$], 3.17–3.22 (m, 1 H, CH), 4.15 (d, *J* = 11.92 Hz, 1 H, Ph_2CH), 6.60–6.67 (m, 4 H, 4 × ArH), 7.11–7.17 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.7, 27.2, 29.0, 29.2, 36.3, 40.6, 40.7, 40.8, 46.2, 49.7, 55.2, 112.8, 112.9, 128.5, 130.9, 131.4, 149.1, 149.2, 214.2 ppm. IR (KBr): ṽ = 2923, 2859, 2805, 1700, 1614, 1522, 1447, 1351, 805 cm^{-1}. HRMS (EI): calcd. for $C_{27}H_{38}N_2O$ [M] 406.2984; found 406.2988. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 0.5 mL/min; t_R = 15.40 min (minor), 17.89 min (major).

Compound 34: Yield 33 mg, 77%; >99:1 *dr*; white solid. $[\alpha]_D^{20}$ = –42 (79% *ee*; *c* = 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.77–1.88 (m, 2 H, CH_2), 1.93–1.98 [m, 1 H, C(H)H], 2.11–2.26 [m, 1 H, C(H)H], 2.40 [dd, *J* = 12.77, 3.78 Hz, 1 H, C(H)H], 2.79 [t, *J* = 12.80 Hz, 1 H, C(H)H], 2.88 [s, 6 H, $N(CH_3)_2$], 2.91 [s, 6 H, $N(CH_3)_2$], 3.01–3.13 (m, 1 H, CH), 3.30–3.34 (m, 1 H, PhCH), 4.30 (d, *J* = 12.07 Hz, 1 H, Ph_2CH), 6.64–6.71 (m, 4 H, 4 × ArH), 7.18–7.24 (m, 4 H, 4 × ArH), 7.26–7.30 (m, 3 H, 3 × ArH), 7.35–7.40 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2, 29.1, 40.6, 40.7, 46.1, 46.3, 50.0, 54.9, 112.9, 113.0, 126.6, 126.7, 128.4, 128.5, 128.7, 144.5, 149.2, 213.4 ppm. IR (KBr): ṽ = 2924, 2859, 2802, 1700, 1613, 1520, 1446, 1351, 805 cm^{-1}. HRMS (EI): calcd. for $C_{29}H_{34}N_2O$ [M] 426.2671; found 426.2676. The enantiomer excess was determined by HPLC analysis with a Chiralpak OD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 0.5 mL/min; t_R = 22.98 min (major), 30.62 min (minor).

Compound 35: Yield 31 mg, 67%; >99:1 *dr*; white solid. $[\alpha]_D^{20}$ = –37 (76% *ee*; *c* = 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.74–1.94 [m, 3 H, CH_2 + C(H)H], 2.05–2.18 [m, 1 H, C(H)H], 2.34 [dd, *J* = 12.71, 3.67 Hz, 1 H, C(H)H], 2.71 [t, *J* = 12.71 Hz, 1 H, C(H)H], 2.86 [s, 6 H, $N(CH_3)_2$], 2.88 [s, 6 H, $N(CH_3)_2$], 2.97–3.08 (m, 1 H, CH), 3.27–3.31 (m, 1 H, PhCH), 4.24 (d, *J* = 12.01 Hz, 1 H, Ph_2CH), 6.60–6.67 (m, 4 H, 4 × ArH), 7.14–7.20 (m, 6 H, 6 × ArH), 7.25–7.32 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 29.0, 40.7, 40.8, 45.6, 46.3, 50.1, 54.9, 112.9, 113.1, 128.1, 128.5, 128.6, 128.9, 130.3, 131.0, 132.44, 143.0, 149.4, 149.4, 213.0 ppm. IR (KBr): ṽ = 2925, 2856, 2798, 1700, 1614, 1520, 1486, 1447, 1348, 808 cm^{-1}. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:4, *v*/*v*); flow rate = 0.5 mL/min; t_R = 20.15 min (major), 21.87 min (minor).

Compound 36: Yield 34 mg, 66%; 91:9 *dr*; white solid. $[\alpha]_D^{20}$ = –51 (69% *ee*; *c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (td, *J* = 7.19, 0.90 Hz, 6 H, 2 × CH_3), 1.64–1.90 (m, 4 H, 2 × CH_2), 2.16–2.26 (m, 1 H, CH), 2.50–2.62 (m, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$], 2.85 [s, 6 H, $N(CH_3)_2$], 3.20–3.24 (m, 1 H, CH), 3.36 (d, *J* = 6.90 Hz, 1 H, CH), 4.13–4.23 (m, 5 H, 2 × OCH_2 + Ph_2CH), 6.57–6.69 (m, 4 H, 4 × ArH), 7.10–7.16 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 24.1, 28.3, 39.5, 40.5, 40.6, 42.8, 49.6, 54.6, 56.6, 61.5, 112.7, 112.9, 128.3, 128.4, 130.3, 130.8, 149.1, 149.2, 167.8, 167.9, 211.9 ppm. IR (KBr): ṽ = 2980, 2935, 2857, 2797, 1750, 1729, 1706, 1613, 1564, 1519, 1479, 1445, 1347, 808 cm^{-1}. HRMS (EI): calcd. for $C_{30}H_{40}N_2O_5$ [M] 508.2937; found 508.2942. The enantiomer excess was determined by HPLC analysis with a Chiralpak AS-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:4, *v*/*v*); flow rate = 1.0 mL/min; t_R = 17.50 min (minor), 30.07 min (major).

Compound 37: Yield 36 mg, 57%; 90:10 *dr*; white solid. $[\alpha]_D^{20}$ = –33 (*c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.94 (m, 4 H, 2 × CH_2), 2.22–2.25 (m, 1 H, CH), 2.51–2.66 (m, 2 H, CH_2), 2.86 [s, 6 H, $N(CH_3)_2$], 2.89 [s, 6 H, $N(CH_3)_2$], 3.19–3.22 (m, 1 H, CH), 3.49 (d, *J* = 4.90 Hz, 1 H, CH), 4.09 (d, *J* = 12.04 Hz, 1 H, Ph_2CH), 5.17 (s, 4 H, 2 × $PhCH_2$), 6.59–6.69 (m, 4 H, 4 × ArH), 7.07–7.12 (m, 4 H, 4 × ArH), 7.30–7.34 (m, 10 H, 10 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 28.3, 39.6, 40.6, 40.7, 42.9, 49.6, 54.7, 56.6, 67.3, 112.8, 113.0, 128.3, 128.3, 128.4, 128.5, 128.5, 128.7, 130.4, 135.2, 149.1, 149.2, 167.6, 167.7, 211.8 ppm. IR (KBr): ṽ = 2926, 2857, 2801, 1734, 1709, 1613, 1519, 1455, 1348, 807 cm^{-1}. HRMS (EI): calcd. for $C_{40}H_{44}N_2O_5$ [M] 632.3250; found 632.3256. We failed to determine the *ee*.

Compound 38: Yield 22.5 mg, 50%; >99:1 *dr*; white solid. $[\alpha]_D^{20}$ = –47.6 (59% *ee*; *c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.62–1.67 (m, 2 H, CH_2), 1.69–1.75 (m, 2 H, CH_2), 2.15–2.30 (m, 2 H, CH_2), 2.19 (s, 6 H, 2 × CH_3), 2.74–2.82 (m, 1 H, CH), 2.87 [s, 6 H, $N(CH_3)_2$], 2.90 [s, 6 H, $N(CH_3)_2$], 3.23–3.30 (m, 1 H, CH), 3.75 (d, *J* = 10.35 Hz, 1 H, CH), 4.11 (d, *J* = 11.83 Hz, 1 H, Ph_2CH), 6.61–6.67 (m, 4 H, 4 × ArH), 7.10–7.16 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 28.8, 29.6, 30.1, 40.0, 40.6, 40.7, 43.5, 49.5, 54.8, 73.9, 112.8, 112.9, 128.3, 128.4, 130.7, 130.8, 149.1, 149.2, 203.0, 203.1, 211.5 ppm. IR (KBr): ṽ = 2933, 2856, 2793, 1695, 1614, 1520, 1482, 1443, 1353, 808 cm^{-1}. HRMS (EI): calcd. for $C_{28}H_{36}N_2O_3$ [M] 448.2726; found 448.2730. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 1.0 mL/min; t_R = 25.83 min (minor), 28.10 min (major).

Compound 39: Yield 33 mg, 75%; >99:1 *dr*; white solid. $[\alpha]_D^{20}$ = –90 (84% *ee*; *c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.53 [m, 1 H, C(H)H], 1.58 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.62–1.80 (m, 2 H, CH_2), 1.87–1.92 [m, 1 H, C(H)H], 2.11–2.18 (m, 1 H, CH), 2.31–2.41 (m, 2 H, CH_2), 2.86 [s, 6 H, $N(CH_3)_2$], 2.88 [s, 6 H, $N(CH_3)_2$], 3.20–3.25 (m, 1 H, CH), 4.03 (d, *J* = 12.07 Hz, 1 H, Ph_2CH), 6.60–6.66 (m, 4 H, 4 × ArH), 7.10–7.14 (m, 4 H, 4 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 22.7, 24.1, 27.8, 40.1, 40.6, 40.7, 48.0, 49.9, 54.3, 90.6, 112.8, 113.0, 128.3, 128.4, 129.6, 130.4, 149.3, 149.3, 211.7 ppm. IR (KBr): ṽ = 2985, 2942, 2884, 2799, 1705, 1613, 1533, 1522, 1479, 1446, 1399, 1348, 807 cm^{-1}. HRMS (ESI): clacd. for $C_{26}H_{36}N_3O_3$ [M + H^+] 438.2757; found 438.2762. The enantiomer excess was determined by HPLC analysis on a Chiralpak AS-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:4, *v*/*v*); flow rate = 1.0 mL/min; t_R = 11.06 min (major), 12.66 min (minor).

Compound 40: Yield 32.5 mg, 99%; white solid. $[\alpha]_D^{20}$ = –9.6 (34% *ee*; *c* = 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3 H, CH_3), 2.89 [s, 6 H, $N(CH_3)_2$], 2.90 [s, 6 H, $N(CH_3)_2$], 3.3 (br., 1 H, OH), 4.27 (d, *J* = 4.38 Hz, 1 H, Ph_2CH), 4.79 (d, *J* = 4.29 Hz, 1 H, CH), 6.63 (d, *J* = 8.70 Hz, 2 H, 2 × ArH), 6.68 (d, *J* = 8.70 Hz, 2 H, 2 × ArH), 7.12 (d, *J* = 8.67 Hz, 2 × ArH), 7.23 (d, *J* = 8.67 Hz, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 40.6, 40.7, 52.1, 80.3, 112.6, 112.8, 127.5, 129.0, 129.7, 130.0, 149.3, 149.5, 209.4 ppm. IR (KBr): ṽ = 3462, 3381, 2951, 2914.88, 2883, 2795, 1716, 1696, 1613, 1520, 1482, 1443, 1351, 794 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{27}N_2O_2$ [M + H^+] 327.2073; found 327.2077. The enantiomer excess was determined by HPLC analysis with a Chiralpak AD-H column; λ = 254 nm; eluent: *i*PrOH/*n*-hexane (1:9, *v*/*v*); flow rate = 1.0 mL/min; t_R = 26.08 min (major), 28.90 min (minor).

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra and HPLC analyses of products **30**–**41**.

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