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Enantioselective Organocatalytic α-Alkylation of Ketones by S_N1-Type Reaction of Alcohols

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The enantioselective α-alkylation reaction of cyclic ketones is described. Our catalyst, based on a "privileged" pyrrolidine ring bearing a chiral thioxotetrahydropyrimidinone ring, is a highly reactive catalyst for cyclic ketones. When this catalyst was coupled with in situ generated carbocations derived from alcohols, the corresponding α-alkylated adducts were obtained in moderate to quantitative yields and low to high enantioselectivities (up to 80 % *ee*). The catalyst loading can be efficiently reduced to 10 %, which is the lowest value reported in the literature for such an organocatalytic transformation.

Introduction

The enantioselective α-alkylation of carbonyl compounds has long been considered a daunting challenge.[1] Before the development of organocatalysis,[2,3] asymmetric phase-transfer catalysis was the sole successful approach, although it mainly dealt with the enantioselective synthesis of α-amino acids by the alkylation of glycine derivatives.[4] The dramatic expansion of the field of organocatalysis has led to a large number of new organic transformations along with the development of novel activation modes.[5] In the early years of organocatalysis, enamine aminocatalysis led to the first successful α-alkylation reactions; however, these were limited to intramolecular transformations.[6] Thus, the intermolecular α-alkylation of carbonyl compounds still remained a challenge, mainly due to the depletion of catalytic activity through the undesired *N*-alkylation of the aminocatalysts. With the introduction of novel activation modes in organocatalysis, namely organo-SOMO and photoredox catalysis, MacMillan and co-workers developed new methodologies that efficiently deliver novel transformations including α-alkylation reactions.[7] Inspired by the elegant contributions of Melchiorre[8] and Cozzi[9] and their coworkers on the α-alkylation of aldehydes by enamine catalysis by S_N1-type reactions, we recently questioned whether it might be possible to expand this methodology to the use of ketones. The sole successful example in the literature documents the use of functionalized chiral ionic liquid (FCIL) organocatalysts as the optimum catalysts to induce high enantioselectivity in this transformation.[10] It has to be highlighted that typical aminocatalysts such as proline, diarylprolinols, α-amino acids and primary amines based on cinchona alkaloids lead to either low reactivity (producing mainly byproducts) or low enantioselectivity.[10] Although FCILs led to good enantioselectivities (up to 87% *ee*), a rather high catalyst loading (25%) was needed for the reaction to be viable and to lead to 80% yield.

Based on our previous experience of organocatalysis,[11] we recognized the possibility of using the pyrrolidine-thioxotetrahydropyrimidinone catalyst **4** as an efficient catalyst for the α-alkylation of ketones. Organocatalyst **4** has been very recently reported to catalyze Michael reactions between cyclohexanone and nitro olefins with low catalyst loadings (1–2.5%).[11] Thus, we envisaged combining its catalytic properties with the well-established generation of stabilized carbocations. Herein, we present our results on the α-alkylation of various cyclic ketones through S_N1-type reaction with alcohols.

Results and Discussion

We envisaged the formation of a nucleophilic enamine through the reaction of thioxotetrahydropyrimidinone **4** with cyclohexanone (**1**), and at the same time the presence of an acid co-catalyst would generate a carbocation from the appropriate alcohol.[9,10,12,13] The coupling of these two reactive intermediates would furnish the desired product (Scheme 1).

In our previous studies with thioxotetrahydropyrimidinone **4**, we found that the presence of 4-nitrobenzoic acid (4-NBA) and water gave the optimum results. Thus, in an initial experiment, the α-alkylated product was produced in 69% yield and 68% *ee* (Entry 1, Table 1). Note that along with the desired product, a small amount of benzhydrol dimer was observed (ca. 5%), in accordance with the litera-

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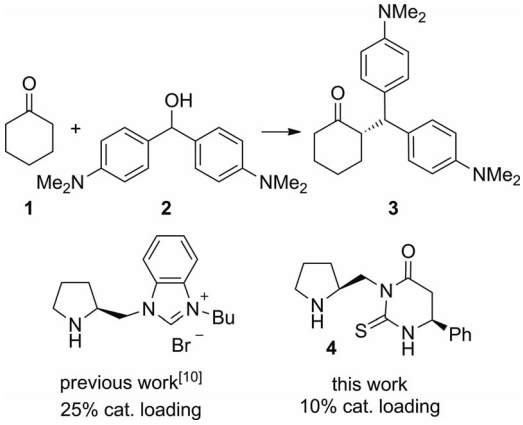
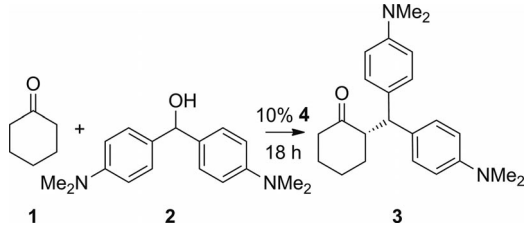


Scheme 1. Organocatalytic α-alkylation of cyclohexanone.

ture.[10] Change of the acid and removal of water did not lead to better results (Entries 2–4, Table 1). As a consequence, the reaction solvent was studied (Entries 5–14, Table 1). Both polar and nonpolar solvents led to decreased yields with few exceptions, and the enantioselectivity of the reaction did not vary significantly. The α-alkylated product was isolated in good to high yields in a small number of solvents, namely chlorinated solvents, EtOAc, Et_2O and toluene. However, other solvents favour the formation of the dimer (ca. 20%), and thus low yields of the desired product were obtained. Dichloromethane afforded the best results, affording a high yield and good *ee*, and no byproduct was observed (Entry 14, Table 1). It is well established in organocatalysis that in some cases lowering of the reaction temperature has a beneficial impact on the enantioselectivity of the reaction. However, in this case, when the reaction was performed at –20 °C, only the benzhydrol dimer was observed (Entry 15, Table 1).

Once dichloromethane was proven to be the solvent of choice, the effect of the nature of the acid co-catalyst was studied (Table 2). First, the appropriate amount of acid to use was explored (Entries 1–7, Table 2). It is clear that an increase of the amount of acid leads to an increase in the amount of in situ generated carbocation. This much faster generation of the carbocation led to lower yields, because the desired transformation competes with the production of the benzhydrol dimer; however, the enantioselectivity of the reaction remained the same (Entries 2–5, Table 2). Thus, it is important to regulate the in situ formation of the carbocation. The use of a smaller amount of acid leads to prolonged reaction times, because the carbocation is generated more slowly. On the other hand, an excess of acid leads to an increased concentration of the reactive carbocation in the reaction medium, which – upon not finding enamine to react with – dimerizes. Bearing this in mind, combined with the fact that there is still unreacted benzhydrol **2** after 18 h, the amount of catalyst was increased to push the reaction to completion, because an increase in the concentration of the in situ formed enamine could lead to full reagent consumption and probably suppress the formation of the dimer. Indeed, a higher yield was observed although the

Table 1. Organocatalyzed reaction between cyclohexanone and benzhydrol **2** in various solvents.[a]

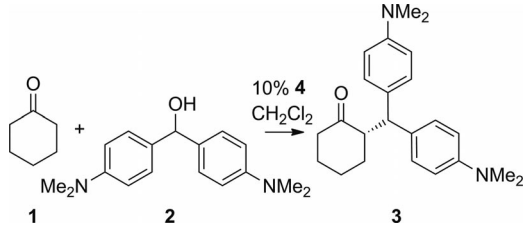


Entry	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1	THF	4-NBA, H_2O	69	68
2	THF	4-NBA	49	64
3	THF	TFA, H_2O	38	62
4	THF	TFA	56	65
5	benzene	4-NBA, H_2O	17	70
6	xylene	4-NBA, H_2O	23	68
7	toluene	4-NBA, H_2O	70	70
8	Et_2O	4-NBA, H_2O	71	67
9	MeCN	4-NBA, H_2O	18	64
10	MeOH	4-NBA, H_2O	6	54
11	EtOAc	4-NBA, H_2O	76	67
12	CH_2ClCH_2Cl	4-NBA, H_2O	71	67
13	$CHCl_3$	4-NBA, H_2O	89	67
14	CH_2Cl_2	4-NBA, H_2O	81	72
15[d]	CH_2Cl_2	4-NBA, H_2O	–	–

[a] Reaction conditions: catalyst **4** (10 mol-%), acid (10 mol-%), H_2O (10 mol-%), solvent (0.2 mL), benzhydrol **2** (0.2 mmol) and cyclohexanone (2 mmol) for 18 h. 4-NBA: 4-nitrobenzoic acid; TFA: trifluoroacetic acid. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC. [d] The reaction was performed at –20 °C for 48 h.

enantioselectivity remained at the same level (Entry 6, Table 2). A prolonged reaction time in the absence of water led to full benzhydrol consumption and the best results with almost quantitative yield (98%) and increased enantioselectivity (80% *ee*, Entry 7, Table 2). Because an acid co-catalyst is required to generate the carbocation, the nature of the acid is certain to play a role in the reaction outcome. Thus, a variety of acids were tested (Entries 8–15, Table 2). Acids with similar acidities [pK_a values in H_2O of 4-nitrobenzoic acid (3.44), 4-cyanobenzoic acid (3.55) and 4-(trifluoromethyl)benzoic acid (3.60)] did not deliver the same levels of reactivity (Entries 7–9, Table 2). These results strengthen our hypothesis that 4-NBA plays a dual role in the reaction by facilitating enamine formation between the catalyst and the ketone as well as the formation of the carbocation. Weaker and stronger acids gave similar results (Entries 10–15, Table 2) although it is worth mentioning that 2,4-dinitrobenzoic acid led to a lower yield due to dimer production (18%) but similar enantioselectivity (Entry 13, Table 2).[14] We assume that 4-NBA forms a unique pairing with the thioxotetrahydropyrimidinone catalyst leading to improved catalytic properties, because acids with similar pK_as do not lead to the same levels of enantioinduction. Similar results are seen in Luo and co-worker's catalytic system in which phthalic acid afforded higher yields than any other acid co-catalyst.[10]

Table 2. Optimization of the nature and amount of the acid co-catalyst.[a]

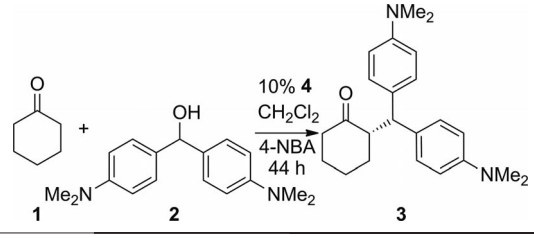


Entry	Additive	Reaction time [h]	Yield [%][b]	*ee* [%][c]
1	4-NBA, H_2O	18	81	72
2	4-NBA (15%), H_2O	18	80	71
3	4-NBA (20%), H_2O	18	61	69
4	4-NBA (50%), H_2O	18	58	71
5	4-NBA (100%), H_2O	18	57	70
6[d]	4-NBA (20%), H_2O	18	88	70
7	4-NBA	44	98	80
8	4-CBA	44	64	70
9	4-TBA	44	62	69
10	PhCOOH	44	17	39
11	HCOOH	44	63	64
12	phthalic acid	44	48	74
13	2,4-DNBA	44	56	74
14	TFA	44	61	42
15	CSA	44	15	58

[a] Reaction conditions: catalyst **4** (10 mol-%), acid (10 mol-%), solvent (0.2 mL), benzhydrol (0.2 mmol) and cyclohexanone (2 mmol). 4-NBA: 4-nitrobenzoic acid, 4-CBA: 4-cyanobenzoic acid, 4-TBA: 4-(trifluoromethyl)benzoic acid, 2,4-DNBA: 2,4-dinitrobenzoic acid, TFA: trifluoroacetic acid, CSA: camphorsulfonic acid. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC. [d] 20 mol-% of catalyst was used.

Furthermore, the effect of the concentration of the reactants was investigated, and it seems to have an impact on both the yield and selectivity (Entries 1–5, Table 3). There is an optimum concentration at which high yields and good enantioselectivities are obtained, because more dilute conditions led to lower yields and an increase in dimer production (22%) and higher concentrations also seemed to have a negative impact on the reaction outcome. A lower yield was obtained when the reaction was carried out neat. At high dilution, the concentration of the nucleophilic enamine is so low that the carbocation, which is formed in situ and is extremely reactive, dimerizes readily leading to lower yields. When there is less solvent, the solvent interactions are weaker, and thus lower yields and *ee*s are obtained. Because commercially available solvents were used and previous experiments had shown a negative impact of water on both the yield and selectivity, we investigated whether a small amount of water was still needed. The use of molecular sieves as well as drying agents led to inferior results (Entries 6 and 7, Table 3). Furthermore, the reaction was performed with freshly distilled CH_2Cl_2 and under an inert gas: diminished yields and selectivities were obtained (Entries 8 and 9, Table 3). It is clear that the small amount of water present in the commercially available solvents helps the reaction, but an increased amount of water has detrimental effects. A lower amount of the ketone, that is, a decrease of the rate of enamine formation, led to lower yields and selectivities accompanied by a small amount of dimer (13%; Entry 10, Table 3), but when the temperature was increased, a lower enantioselectivity was observed (Entry 11, Table 3). Lowering of the catalyst loading to 5% led to a drop in the yield to 61% (Entry 12, Table 3). This procedure differs from the literature procedure[10] in the use of dichloromethane as solvent instead of 1,2-DCE and an equimolar amount of 4-NBA instead of a slight excess of phthalic acid. Furthermore, the use of only 10 mol-% catalyst to afford the optimum results is the main advantage of the current methodology; in literature procedures the use of no less than 25 mol-% catalyst can be expected.

Table 3. Effect of concentration and other factors on the reaction between cyclohexanone and benzhydrol **2**.[a]



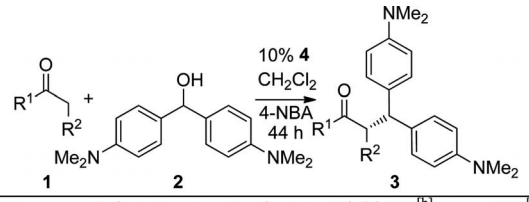
Entry	CH_2Cl_2 [mL]	Yield [%][b]	*ee* [%][c]
1	0.2	98	80
2	0.4	48	65
3	0.1	89	78
4	0.05	68	74
5	0	71	70
6[d]	0.2	61	68
7[e]	0.2	81	70
8[f]	0.2	68	77
9[f,g]	0.2	78	70
10[h]	0.2	68	70
11[i]	0.2	82	48
12[j]	0.2	61	78

[a] Reaction conditions: catalyst **4** (10 mol-%), 4-NBA (10 mol-%), CH_2Cl_2 (0.2 mL), benzhydrol **2** (0.2 mmol) and cyclohexanone (2 mmol) for 44 h. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC. [d] The reaction took place in the presence of 4 Å molecular sieves. [e] The reaction took place in the presence of Na_2SO_4. [f] Dry CH_2Cl_2 was used. [g] The reaction was performed under inert conditions. [h] Ketone/benzhydrol, 5:1. [i] The reaction was performed at reflux temperature. [j] 5 mol-% catalyst was used.

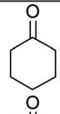
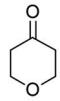
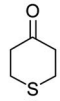
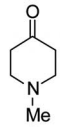
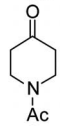
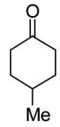
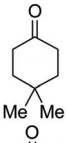
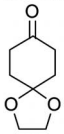
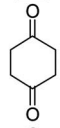
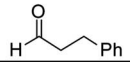
Once the optimum reaction conditions had been found, we became interested in exploring the scope and limitations of the thioxotetrahydropyrimidinone catalyst in the α-alkylation reactions of ketones (Table 4).[15] Cyclic ketones bearing heteroatoms such as oxygen and sulfur afforded the desired products (**3b** and **3c**) in high yields and with good enantioselectivities (Entries 2 and 3, Table 4), whereas nitrogen-containing cyclic ketones led to lower yields and selectivities (Entries 4 and 5, Table 4). Desymmetrization of 4-monosubstituted cyclohexanones was also possible, pro-

ducing a single diastereomer (**3f**) in high enantioselectivity and moderate yield (Entry 6, Table 4). Disubstituted cyclohexanones were well tolerated, albeit giving lower yields and selectivities in accordance with previous observations (Entries 7 and 8, Table 4).[10] A prolonged reaction time was required for much more difficult substrates (Entries 9 and 10, Table 4). 1,4-Cyclohexanedione led to high yields but low selectivities, whereas cyclopentanone, which has not been reported to produce the desired alkylated product by any other means,[10] was alkylated in low yield and low enantioselectivity. Finally, when ketones were replaced by aldehydes (for example, 3-phenylpropanal), excellent yield but low enantioselectivity were observed (Entry 11, Table 4). When 1,4-cyclohexanedione was replaced by 1,2-cyclohexanedione (**5**), an inseparable mixture of products **6** and **7** was isolated (Scheme 2); The desired alkylated product **7** was obtained in low yield along with the product derived from *O*-alkylation of the enolate.

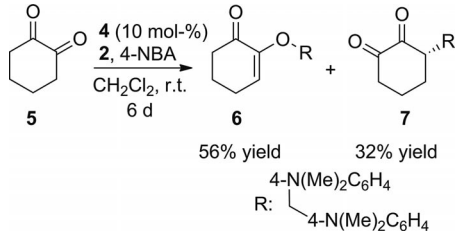
Table 4. Enantioselective α-alkylation of ketones by S_N1 alkylation of benzhydrol **2**.[a]



1 2 3

Entry	Substrate	Product	Yield [%][b]	*ee* [%][c]
1		**3a**	98	80
2		**3b**	88	67
3		**3c**	79	71
4		**3d**	30	16
5		**3e**	44	30
6		**3f**	52	78
7		**3g**	44	42
8		**3h**	62	44
9[d]		**3i**	85	25
10[d]		**3j**	21	28
11		**3k**	96	16

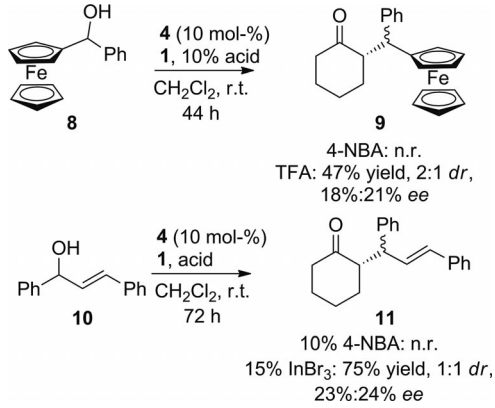
[a] Reaction conditions: catalyst **4** (10 mol-%), 4-NBA (10 mol-%), CH_2Cl_2 (0.2 mL), benzhydrol **2** (0.2 mmol) and ketone (2 mmol) for 44 h. [b] Isolated yield after column chromatography. [c] The *ee* was determined by chiral-phase HPLC. [d] Reaction time: 6 d.



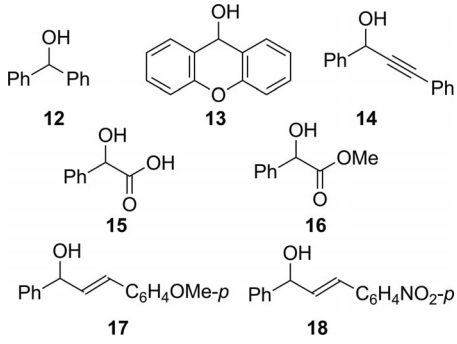
Scheme 2. Organocatalytic α-alkylation reaction of benzhydrol **2** with 1,2-cyclohexanodione.

To further expand the reaction scope and discover the limits of this methodology, the carbocation was replaced (Schemes 3 and 4). On consideration of Mayr's electrophilicity scale,[16] ferrocenyl-derived alcohol **8** was employed, but no reaction took place (Scheme 3, top). However, when 4-NBA was replaced by TFA, **9** was isolated in a moderate yield and with low diastereoselectivity and low enantioselectivity (18% *ee* for the major diastereomer and 21% *ee* for the minor diastereomer). However, these results are the best having been obtained with the ferrocenyl substrate, because the highest selectivities reported in the literature are 8 and 18% *ee*, respectively.[10] In the alkylation of ketones, only secondary alcohols, the corresponding carbocations of which are stabilized by two electron-rich aromatic moieties, have been used. In contrast, in the case of aldehydes, there are a few reports of secondary alcohols bearing aryl and alkenyl moieties having been employed in the presence of $InBr_3$ leading to α-allylated aldehydes.[17] Thus, 1,3-diphenylprop-2-en-1-ol (**10**) was used as the carbocation precursor (Scheme 3, bottom). When 4-NBA was used, no reaction took place. In contrast, the use of $InBr_3$ led to a high yield with 1:1 diastereoselectivity, as expected,[17] and low enantioselectivity. Although the enantioselectivity was low, this is the first example of such a reaction between cyclic ketones and aryl-allyl alcohols performed under organocatalysis.[18,19] When the electron-rich substituents were removed and simple benzhydrol (**12**) was used, no reaction took place (Scheme 4). In the case of xanthol (**13**), although the product can be observed in the ^1H NMR spectrum of the crude mixture, the α-alkylated adduct was probably unstable under silica gel purification and decomposed (Scheme 4). Furthermore, the corresponding alkynyl derivative **14**, which has been used successfully with aldehydes,[20] was used, albeit with no success (Scheme 4). Stabilization of the carbocation formed from an alcohol bearing an aro-

matic moiety and a carboxylic derivative was also envisaged (Scheme 4). However, the use of mandelic acid (**15**) and methyl mandelate (**16**) did not lead to the desired product. To shed more light on this interesting allylation reaction, alcohols **17** and **18** were used. Unfortunately, in both cases complicated mixtures were obtained. In the case of **17**, at least three different isomers of the desired product could be identified in the reaction mixture; however, the yield was low. In the case of **18**, the reaction mixture was so complicated that we could not identify any desired product.

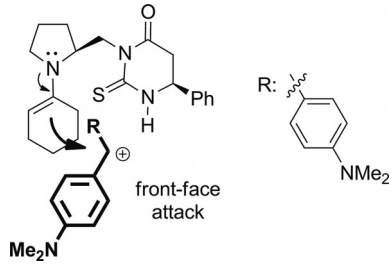


Scheme 3. Succesful examples of organocatalytic α-alkylation reactions of cyclohexanone with alcohols.



Scheme 4. Alcohols used unsuccesfully in this study.

To account for the stereochemical outcome of the reaction, a possible mechanism is proposed in Scheme 5. Initially, the catalyst binds to the ketone to form a nucleophilic enamine. Once the carbocation has been generated, the thioxotetrahydropyrimidinone ring may either facilitate the alkylation from the front face through stabilizing interactions between the ring and the carbocation or from the back face as a result of steric hindrance of the front face. Luo and co-workers assumed their ionic catalyst efficiently blocks the front face and that addition occurs from the back face.[10] Because the same enantiomer was obtained as in the Luo and co-workers' catalytic system,[10] we assume that the s-*trans* enamine of the cyclic ketone, which is more stable and suffers from the least steric interactions, couples to the carbocation. To obtain the correct enantiomer of the product, the carbocation must react from the front side. We assume that the carbocation is positioned there through stabilizing interactions from the thioxotetrahydropyrimidinone ring of the catalyst.[11] The best results were obtained by using an equimolar amount of acid with respect to the catalyst. We assume that a sacrificial amount of acid is enough for the catalyst to assimilate the ketone and produce the nucleophilic enamine. The rest of the acid is used to generate the carbocation, which is coupled to the enamine. Furthermore, because thioxotetrahydropyrimidinone **4** does not have an ionic-liquid-type structure but still catalyzes the reaction as efficiently as the ionic catalyst of Luo and co-workers, it is likely that their ionic-liquid-type catalyst is not involved in any interaction with the carbocation other than shielding efficiently one of the potential faces of addition.



Scheme 5. Proposed mechanism for the α-alkylation of ketones.

Conclusions

The first example of a non-ionic-liquid-type organocatalyst that can catalyze the "difficult" α-alkylation of ketones has been reported herein. The reduced catalyst loading (10 vs. 25 mol-%) is the main advantage of the thioxotetrahydropyrimidinone catalyst **4** over the previously known catalyst system[10] providing similar yields and selectivities. An effort to acquire a better understanding of the reaction mechanism and the development of new applications are under way.

Experimental Section

General Procedure for the α-Alkylation of Ketones by S_N1 Reaction of Alcohols: 4-Nitrobenzoic acid (1.74 mg, 0.01 mmol) was added to a stirred solution of catalyst **4** (3 mg, 0.01 mmol) in CH_2Cl_2 (0.2 mL). Alcohol (0.10 mmol) was added followed by cyclohexanone (0.10 mL, 1.00 mmol). The reaction mixture was stirred for 44 h. The solvent was evaporated, and the crude product was purified by flash column chromatography eluting with an appropriate mixture of petroleum ether (40–60 °C)/EtOAc to afford the desired product.

(*S*)-2-{Bis[4-(dimethylamino)phenyl]methyl}cyclohexanone:[10] Table 4, Entry 1. White solid. Yield 98%; m.p. 156–159 °C. $[\alpha]_D^{20}$ = –98.0 (*c* = 0.025, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.15–7.05 (m, 4 H, ArH), 6.70–6.60 (m, 4 H, ArH), 4.17 (d, *J* = 11.5 Hz, 1 H, $CHAr_2$), 3.29–3.18 (m, 1 H, CHCO), 2.91–2.82 [m, 12 H, 2 $N(CH_3)_2$], 2.53–2.23 (m, 2 H, CH_2CO), 1.98–1.76 (m, 4 H, 2 CH_2), 1.68–1.44 (m, 2 H, CH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.3, 148.8, 148.6, 132.3, 131.7, 128.6, 128.0, 112.7, 55.3, 48.8, 41.9, 40.6, 32.8, 29.1, 23.6 ppm. MS (ESI): *m*/*z* (%) = 351 (100) $[M + H]^+$. The enantiomeric excess was determined by HPLC analysis on a

Chiralpak AD-H column [eluent: *i*PrOH/*n*-hexane (5:95), flow rate 0.3 mL/min; t_R = 68.09 min (minor), t_R = 76.24 min (major).

Supporting Information (see footnote on the first page of this article): Full experimental details, NMR spectra and HPLC data.

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