α-Hydroxy Ketones as Masked Ester Donors in Brønsted Base-Catalyzed Conjugate Additions to Nitroalkenes

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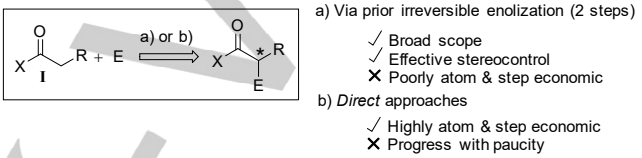
Abstract: The catalyst-controlled enantioselective direct addition reaction of enolizable esters and related carboxylic acid derivatives to π-electrophiles remains a difficult synthetic transformation. In this study, the suitability of α-hydroxy ketones as ester equivalents capable to be activated by bifunctional Brønsted base catalysts in the context of conjugate addition reactions to nitroolefins is demonstrated. The scope of the reaction, which affords the corresponding Michael adducts with very high stereoselectivity (dr ≥95:5, up to 99% ee). and its limitations are explored, as is the aftermath elaboration of adducts into densely functionalized enantioenriched products.

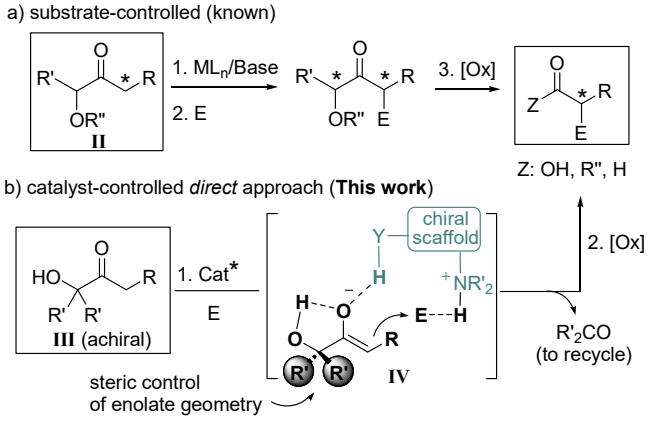
Introduction

The addition of an enolizable carbonyl compound to a π-electrophile represents a fundamental entry to new carbon-carbon bonds, resulting in synthetically useful α-modified carbonyl compounds. Stereoselective variants involving an enolizable substrate in the carboxylic acid oxidation state and using chiral stoichiometric reagents and auxiliaries have been well established, but commonly require a previous, irreversible enolization step (Scheme 1a).[1] In contrast, direct protocols (that is, without a separate enolization process and consumption of stoichiometric base) involving enolizable esters, amides or the like and a chiral catalyst are less developed (Scheme 1b). Catalytic activation of esters and ester-like substrates is challenging owing to their diminished carbon acidity. Some progress in the area has been made involving enolizable thioamides/lactams,[2] amides,[3] nitriles,[4] imides,[5] and free carboxylic acids[6] in which a chiral metallic catalyst in combination with sub-[2-4] or superstoichiometric[5-6] base is used. The covalent activation of carboxylic acids and esters by chiral NHC and isothiourea catalysts has also been reported to afford lactone- and lactam-type cyclic products mainly.[7] In addition, seldom examples of Brønsted base catalyzed, noncovalent activation of reactive ester equivalents (acyl silanes and phosphonates, thioesters, pyrazoleamides, cyclic anhydrides) have been documented.[8,9] However, in many instances control of the reaction diastereo- and enantioselectivity is still a challenge.



Scheme 1. State of the art of asymmetric α-functionalization of carboxylic acid derivatives (E: electrophile; X: heteroatom).

While all these studies deal with enolizable substrates of the type **I** (acyl–heteroatom systems), a conceptually different, but in practice equivalent, strategy involves the use of α-hydroxy ketones as carboxylic acid surrogates. Early work by the groups of Heathcock[10] and Masamune,[11] independently, established a route to α-modified carboxylic acids upon an enolization/α'-functionalization/ketol scission sequence starting from chiral α-hydroxy ketones **II** (Scheme 2a). More recently, the approach was further advanced so that the chiral information source was no longer sacrificially destroyed during ketol oxidative scission.[12] Moreover, the scission step is ease to modify in order to access the corresponding ketone and aldehyde products as well. However, and despite its potential and practicality, to our knowledge no direct version of this approach relying on a combination of an *achiral* α-hydroxy ketone and a suitable chiral



Scheme 2. α-Hydroxy ketones as donor carboxylic acid equivalents.

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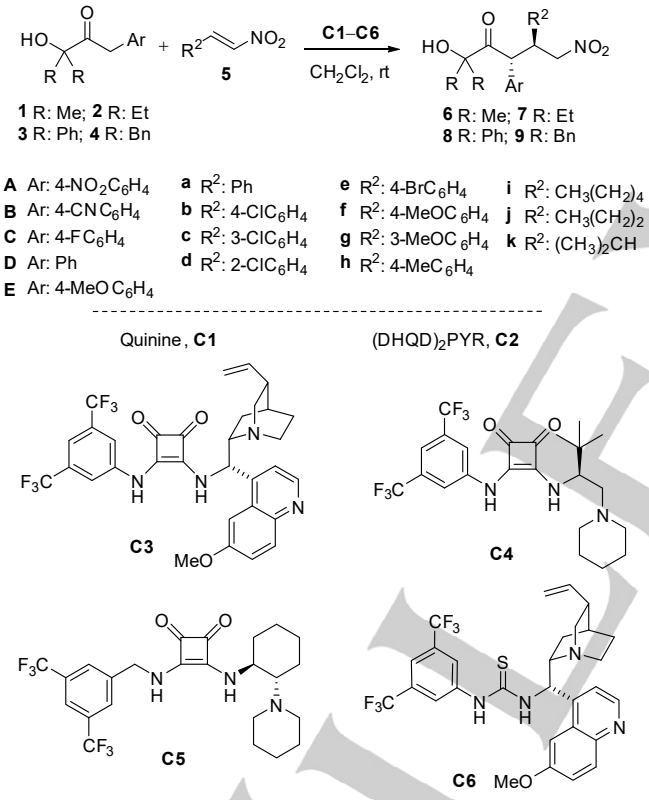
catalyst, has been reported so far. Here we show that *achiral* α-hydroxy ketones **III** react smoothly with nitroalkenes in the presence of bifunctional Brønsted base catalysts to afford the corresponding Michael adducts in high stereoselectivity. This constitutes the first demonstration of *achiral* α-hydroxy ketones as ester and aldehyde donor equivalents in the context of asymmetric catalysis.[13]

Results and Discussion

The underlying idea is that substrate **III** may get activated by a bifunctional tertiary amine/H-bond donor catalyst as in model **IV** to ultimately attack a suitable π-electrophilic reaction partner and lead, after final ketol scission, to enantioenriched α-branched carboxylic acids and derivatives. For initial validation of the idea the reaction of α-hydroxy ketone **1A** with nitroalkene **5a** was selected and several Brønsted bases were screened.



Scheme 3. Conjugate addition of α-hydroxy ketones to nitroalkenes catalyzed by Brønsted bases **C1**–**C6**.

As the results in Table 1 show, both quinine **C1** and $(DHQD)_2PYR$ **C2** were able to promote the addition reaction thus demonstrating the feasibility of α-hydroxy ketones for activation with mild bases, but led to suboptimal enantioselectivity (entries 1 and 2). Among several bifunctional catalysts examined, the squaramide **C3**[14] provided after 5 h at room temperature the addition adduct **6Aa** in nearly quantitative yield, but with yet unsatisfactory selectivity (entry 3). Catalysts **C4**[15] and **C5** behaved similarly, both affording slightly better enantiocontrol (70% and 69% *ee*, respectively; entries 4 and 5). Finally, the thiourea catalyst **C6**[16] resulted superior in this reaction affording a product of 80% *ee* (entry 6). Then, the influence of the two R groups at the Cα of the ketol substrate, which can be readily prepared through the method of Qi from the corresponding alkyne, CO_2 and simple ketones as starting materials,[17] was examined. When moving from **1A**(R=Me) to **2A**(R=Et) and **3A**(R=Ph) there is not much impact on the reaction selectivity (compare entries 3-5 with 6-8, and 9). However, the reaction employing **4A**(R=Bn) led to an outstanding 99% *ee* using either catalyst **C3** or **C6** (entries 10 and 12). Of importance, in all the above experiments essentially a single diastereomer was observed by ^1H NMR (dr ≥95:5).

Table 1. Screening of catalysts and ketol template for the reaction with **5a**.[a]

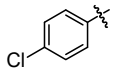
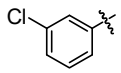
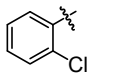
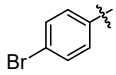
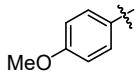
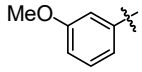
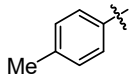
Entry	Reaction	Catalyst	Time [h]	Yield [%][b]	*ee* [%][d]
1		**C1**	72	97	10[e]
2		**C2**	72	86	–50[e]
3	**1A** + **5a** → **6Aa** (cat; R: Me)	**C3**	5	98	60
4		**C4**	72	97	70
5		**C5**	72	96	69
6		**C6**	72	98	80[e]
6		**C3**	24	97	76
7	**2A** + **5a** → **7Aa** (cat; R: Et)	**C4**	48	55[c]	72
8		**C6**	24	97	80
9	**3A** + **5a** → **8Aa** (cat; R: Ph)	**C6**	24	87	80
10		**C3**	24	75	99
11	**4A** + **5a** → **9Aa** (cat; R: Bn)	**C4**	72	70[c]	88
12		**C6**	24	99	99

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of ketone/**5a**/catalyst 1:2:0.1); dr >95:5 in all entries as determined by ^1H NMR (300 MHz) of crude sample. [b] Yields of isolated product after chromatography. [c] Conversion; yield not determined. [d] Determined by chiral HPLC analysis. [e] Reaction performed at –20 °C.

Based on the above results, α,α-dibenzyl α-hydroxy ketone **4A** and catalyst **C6** were selected for exploring the scope of the reaction regarding the nitroalkene component. As data in Table 2 show, several β-aryl substituted nitroalkenes including electron-poor (entries 1–4) and electron-rich (entries 5, 6, 7) systems participate in the reaction with **4A** to afford the corresponding products **9A** in good yields and essentially perfect stereocontrol (dr ≥95:5, 99% *ee*) in all cases. Importantly, the more challenging alkyl-substituted nitroalkenes, such as **5i** and **5j**, were also competent reaction partners affording the corresponding adducts **9Ai** and **9Aj** in 75% and 76% yields, diastereomeric ratios of ≥95:5, and *ee*'s of 96% and 99%, respectively. In these instances, elapsed times were needed for useful conversion. With the more demanding isopropyl nitroalkene **5k** reactivity was an issue, but selectivity remained still high (90:10 dr, 97% *ee* for the major diastereomer).

Next the reaction scope with respect to the α'-aryl substituent of the α-hydroxy ketone was studied. As data in Table 3 show, the

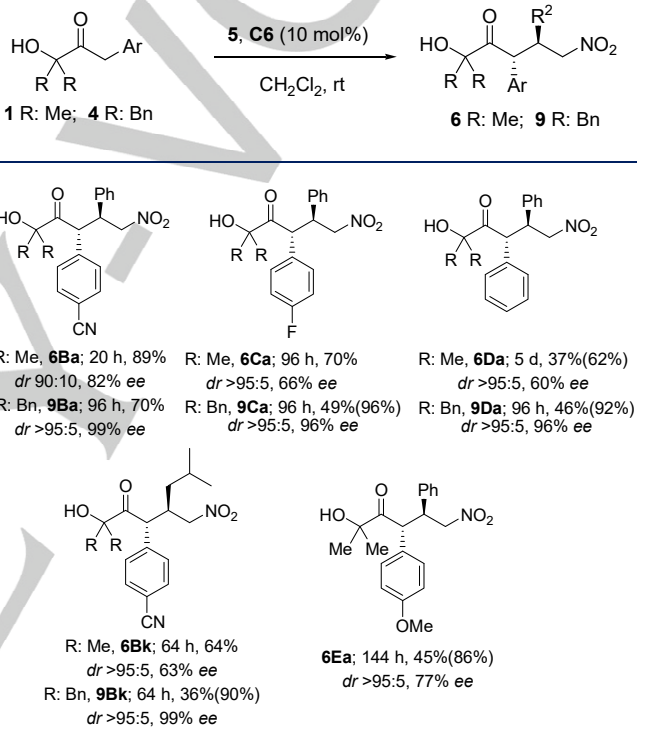
Table 2. Scope of the reaction of **4A** with nitroalkenes **5** catalyzed by **C6**.[a]

Entry	Nitroalkene	R^2	Product	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**5b**		**9Ab**	16	86	>95:5	99
2	**5c**		**9Ac**	16	81	>95:5	99
3	**5d**		**9Ad**	16	77	>95:5	99
4	**5e**		**9Ae**	16	93	>95:5	99
5	**5f**		**9Af**	16	92	>95:5	99
6	**5g**		**9Ag**	16	80	>95:5	99
7	**5h**		**9Ah**	16	85	>95:5	99
8	**5i**	$CH_3(CH_2)_4$	**9Ai**	72	75	>95:5	96
9	**5j**	$CH_3(CH_2)_2$	**9Aj**	44	76	>95:5	99
10	**5k**	$(CH_3)_2CH$	**9Ak**	120	45(75)[e]	90:10	97

[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of **4A**/**5**/catalyst, for R^2=aromatic, 1:2:0.1; for R^2=aliphatic, 1:3:0.2) at r.t. unless otherwise stated. [b] Yields of isolated product after chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC analysis using a chiral stationary phase. [e] Yield in parentheses based on recovered starting material.

reaction tolerates electron-poor, neutral or rich aryl substituents. However, in the latter case the reaction proceeded very slowly. For instance, the reaction with nitrostyrene of hydroxy ketone **4B**, bearing at Cα' a *p*-cyanophenyl group, proceeded to completion in about 96 hours, affording adduct **9Ba** in good yield as essentially single isomer. Reactions of the *p*-fluorophenyl and phenyl analogs **4C** and **4D** were incomplete after 96 h (49% and 46% isolated yields, respectively), although selectivity remained high in both cases (>95:5 dr; 96% *ee*). In its turn the reaction of α'-*p*-methoxyphenyl ketone **4E** resulted impractical. However, the *gem*-dimethyl analog **1E** could react with nitrostyrene affording adduct **6Ea** as single diastereomer in 45% yield (86% based on recovered starting material) and 77% *ee*. These experiments show again the influence of the ketol R group, with the sterically more demanding α,α-dibenzyl ketols **4** requiring longer reaction times as compared with the α,α-dimethyl congeners **1**, but leading to considerably better diastereo- (dr≥95:5) and enantioselectivities (96%–99% *ee*). Importantly, high selectivity was also attained in the reaction of **4B** involving the β-isobutyl-substituted nitroalkene **5k**, which afforded adduct **9Bk** as single diastereomer and 99% *ee*. The absolute configuration of adduct **9Ab** was established by single crystal X-ray structure analysis[18] and that of the remaining adducts by analogy and by assuming a uniform reaction mechanism.

Table 3. Scope of the reaction regarding the α-hydroxy ketone.[a]



[a] Reactions conducted on a 0.1 mmol scale in 0.3 mL CH_2Cl_2 (molar ratio of ketone/**5a**/catalyst 1:3:0.1 or 1:1.2:0.1). Yields in parentheses based on recovered starting material.

Based on the most accepted TS models for conjugate addition reactions catalyzed by these types of (thio)urea bifunctional catalysts, in which protonated quinuclidine activates the electrophile,[19] stereomodel **V** may be invoked to account for the observed reaction outcome (Figure 1a). The active role played by the free hydroxy group of the template **1A** is apparent if reaction conversions are compared with those obtained with the *O*-$SiMe_3$ derivative **1A'**. As control experiments in Figure 1b show, while the **C6**-catalyzed reaction of nitrostyrene with **1A** to produce **6Aa** is essentially over after 10 h at room temperature, the reaction involving **1A'** progressed much more slowly, with around 50% conversion reached after 20 h. Same trend was observed for the reaction of the *O*-$SiMe_3$ derivative of **1B**.[20]

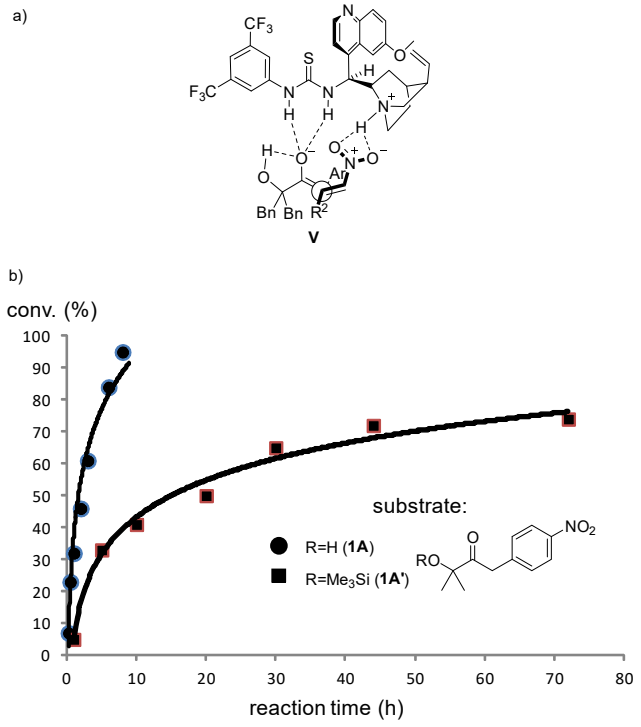
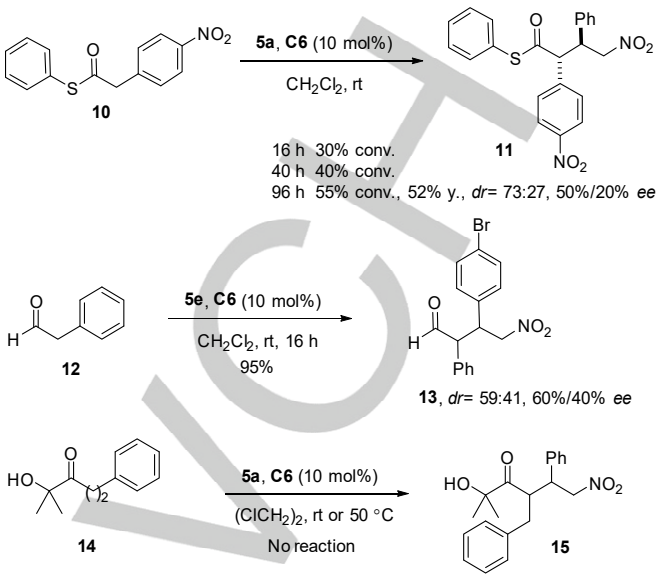


Figure 1. a) Proposed stereomodel. b) Progress of the **C6**-catalyzed reaction of nitrostyrene (**5a**) with **1A** and its *O*-TMS derivative **1A'**, respectively.

Additional control experiments using as donor component the related (thio)esters and aldehydes (Scheme 4) further demonstrated the importance of the α-hydroxy ketone template in this development. For example, methyl *p*-nitrophenylacetate did not react at all with nitrostyrene in methylene chloride in the presence of catalyst **C6** (10 mol%).[21] In its turn, the more reactive thioester[8c,d] **10** hardly reacted under the same conditions to reach a maximum 55% conversion after 96 h, giving rise to product **11** with poor selectivity. As expected, the reactivity was not a problem with phenylacetaldehyde **12**, but the resulting aldehyde **13** is configurationally unstable and an almost equimolar mixture of epimers was isolated. One limitation of the method is the unsuitability of α-hydroxy ketones with decreasing α'-carbon acidity, such as **14**, which remained intact after 24 h under the above catalytic conditions (or even at 50 °C). In this respect, we have recently found that the related β',γ'-unsaturated ketols, which upon enolization would form a vinylogous enolate, are competent substrates for this reaction with nitroolefins.[22] Additionaly, thus generated vinylogous enolates proved to react with high regio- (α vs. γ) and stereoselectivity. At this stage we set out to complement these previous studies with additional entries and establish which type of ketol substructure is optimum with respect to both reactivity and selectivity. As the results in Table 4 show, the catalyzed reaction of ketones **16** and **17** with nitroalkene **5a** proceeded virtually to completion within a few hours at room temperature, affording the corresponding Michael adducts **19** and **20**, although accompanied with variable amounts of the corresponding γ-regioisomers **19'** and **20'** (Table 4, entries 1–4). For these reactions catalyst **C5** was more active than **C6**

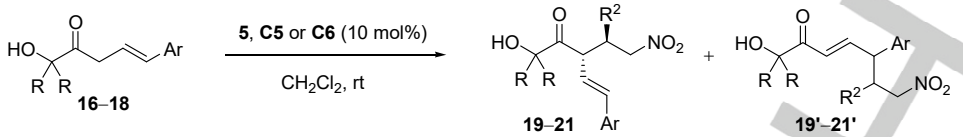


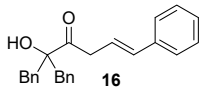
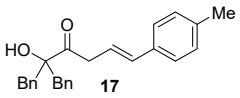
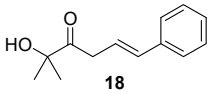
Scheme 4. Unsuitable ketone and thioester substrates.

while both provided high levels of diastereo- and enantiocontrol (essentially single stereoisomer isolated). However, neither catalyst was able to control the α- vs. γ-regioselectivity properly (product ratios from 41:59 to 74:26 at best). Experiments using the parent gem-dimethyl ketone **18** instead demonstrated once again that this regioselectivity issue could be properly addressed. With this ketol substrate, and using catalyst **C6**, mixtures of the corresponding α– and γ–adducts **21**/**21'** were obtained again (entries 6, 8, 10, 12). However, using catalyst **C5** the corresponding adduct **21** could be obtained exclusively. For instance, the reaction of **18** with **5a** afforded **21a** in 85% isolated yield, as essentially single diastereomer and 97% *ee* (entry 5). This pattern was reproduced with other nitroalkenes **5b,c,f,i**, giving rise to the corresponding adducts **21** as clean products with high isolated yields, essentially perfect diastereoselectivity, and *ee*'s in the 94%-98% range (entries 7, 9, 11, 13).

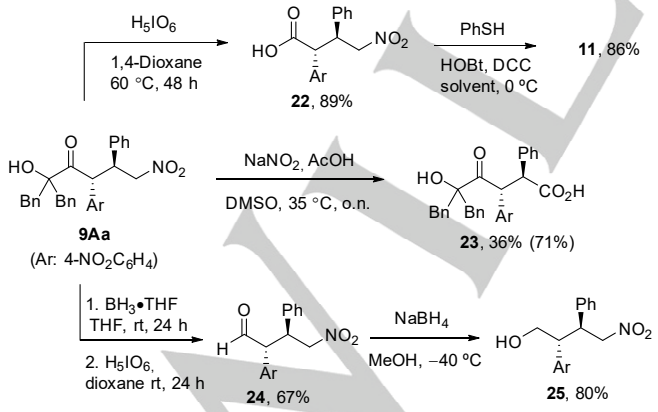
Adducts obtained through the above catalytic reactions may serve as versatile platform in synthesis. For instance, Scheme 5, the oxidative cleavage of the ketol moiety in **9Aa** by treatment with H_5IO_6 afforded the arylacetic acid **22** in 89% yield, along with dibenzyl ketone as the only organic side product which could be recovered and reused.[23] Compound **22** was then transformed into the phenylthio ester **11** under usual conditions. Thus, the lack of reactivity and selectivity associated with simple arylacetic esters and thioesters may be circumvented using α-hydroxy ketones as donor ester equivalents. Alternatively, reduction of the ketol carbonyl in **9Aa** with borane and subsequent treatment with H_5IO_6 as above gave aldehyde **24** in 67% yield over the two steps. It should be noted that in no case was epimerization at the α-carbon observed, an important feature of the present approach considering the high tendency of these compounds (i. e. arylacetic aldehydes, vide supra) towards base-promoted isomerisation. On the other hand, the C–NO_2 group in compound **9Aa** could be oxidized under Mioskowski conditions[24] without affecting the

Table 4. Alkenyl ketols **16**–**18** as ester donor equivalents.[a]



Entry[b]	Ketol substrate	Nitroalkene, R^2	Product	Cat	T [°C]	Time [h]	α/γ Ratio	Yield [%][c]	*dr*[d]	*ee* [%][e]
1		**5a**, Ph	**19/19'**	**C5**	20	2	72:28	63	>95:5 / >95:5	>98 / 84
2	**16**			**C6**	20	2	41:59	35	>95:5 / >95:5	>98 / 94
3		**5a**, Ph	**20/20'**	**C5**	20	2	74:26	70	>95:5 / >95:5	98 / >98
4	**17**			**C6**	20	16	44:56	38	>95:5 / >95:5	98 / >98
5		**5a**, Ph	**21a/21'a**	**C5**	20	2.5	>98:2	85	>95:5 / --	97 / --
6				**C6**	–10	20	86:14	68	>95:5 />95:5	95 / ND
7		**5b**, 4-ClC_6H_4	**21b/21'b**	**C5**	20	2.5	>98:2	82	>95:5 / --	95 / --
8				**C6**	–10	14	68:32	60	>95:5 />95:5	83 / 66
9		**5c**, 3-ClC_6H_4	**21c/21'c**	**C5**	20	3	>98:2	91	>95:5 / --	96 / --
10	**18**			**C6**	–20	16	61:39	57	>95:5 / >95:5	81 / 71
11		**5f**, 4-$MeOC_6H_4$	**21f/21'f**	**C5**	20	2.5	>98:2	75	>95:5 / --	94 / --
12				**C6**	–20	16	96:4	77	>95:5 / --	87 / ND
13		**5i**, $CH_3(CH_2)_4$	**21i/21'i**	**C5**	20	14	>98:2	94	>95:5 / --	98 / --

[a] Reactions conducted on a 0.2 mmol **18** in 0.3 mL CH_2Cl_2 at r.t. unless otherwise stated. Molar ratio of **18**/**5**/catalyst, 1.5:1:0.1 (for **C6**); 1:1.1:0.05 (for **C5**). [b] For entries 5, 7 and 11, see Ref 22. [c] Yields of isolated isomers **19**-**21** after chromatography. [d] Determined by ^{1}H NMR. [e] Determined by HPLC analysis using a chiral stationary phase. ND: Not determined.

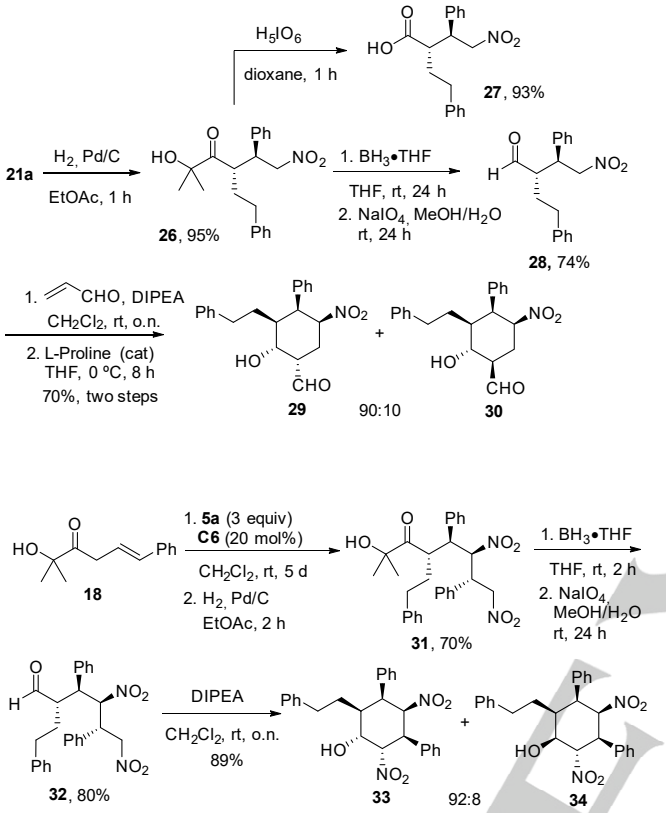


Scheme 5. Scission of ketol and nitro moieties of adducts.

ketol moiety to deliver the carboxylic acid **23**. First oxidation run was incomplete (36%), but by applying further oxidation runs to the recovered unoxidized material, product **23** was isolated in a combined 71% yield.

One particular advantage of the high regio- and stereoselectivity observed in the reactions with β',γ'-unsaturated ketols is that a simple hydrogenation of the C=C double bond in the resulting adducts (e.g. **21a**, Scheme 6) gives access to compounds like **26** which are otherwise difficult to obtain (formally derived from less acidic ketones, see above). Then, ketol scission as above would provide the corresponding acid **27** or aldehyde **28** in high yields. With aldehyde **28** at hand, a suitable Michael/aldol domino process[25, 26] involving acrolein as reaction pattern allowed the fully enantiocontrolled construction of densely substituted cyclohexanecarbaldehydes **29** and **30** in 70% combined yield and a 90:10 ratio.[27] This ratio turned to be temperature-dependent and when the reaction mixture was warmed to room temperature and stirred for 2 h, the ratio of isomers **29** and **30** obtained was 65:35. This observation might suggest that the intramolecular aldol process becomes increasingly reversible at temperatures above 0 °C or, alternatively, proline is able to epimerize **29** unless temperature is kept low. Similarly, hydrogenation of the adduct resulting from a **C6**-catalyzed double Michael reaction of **18** gave rise the branched aliphatic ketone **31** which was transformed into aldehyde **32** in 80% yield over two steps. Final treatment of **32**

with DIPEA smoothly afforded the corresponding hexasubstituted cyclohexanes **33** and **34** in a 92:8 ratio and combined 89% yield.[28] Configuration of cyclic products **29/30** and **33/34** was preliminary established by correlation of the H-H coupling constants in their ^{1}H NMR spectra, and then confirmed by a single crystal X-ray analysis of **33**.[20]



Scheme 6. Further possibilities for elaboration of adducts.

A distinguishing feature of the two reaction sequences in Scheme 6 is that both aldehydes **28** and **32** have a relative α/β *anti* configuration. Accordingly, this approach complements previous syntheses of related cyclohexane systems based on enamine mediated domino processes[27, 28] which proceeded via the corresponding aldehydes with relative α/β *syn* configuration instead.

Conclusions

In conclusion, enolizable α-hydroxy α,α-disubstituted ketones are introduced as efficient ester and aldehyde donor equivalents in asymmetric catalysis. The reactivity and stereoselectivity profile of these templates can be easily modulated by varying the size of the geminal R substituents at Cα, with the α,α-dibenzyl-substituted congeners providing the best enantiocontrol with the selected reaction and catalysts. Specifically, their conjugate addition reaction to nitroalkenes, including the challenging β-alkyl-substituted nitroalkenes, proceeds smoothly under bifunctional Brønsted base catalysis to afford adducts with very high diastereo- and enantioselectivity (dr ≥95:5, up to 99% *ee*). Elaboration of the resulting adducts via smooth oxidative ketol cleavage gives access to the corresponding enantioenriched α-branched carboxylic acid and aldehyde products, *inter alia* aryl acetics,[29] along with dibenzylacetone byproduct which can be separated and recycled. Additional reaction sequences are also applicable to construct densely functionalized carbocycles with complementary relative configuration as compared with previous methods based on enamine catalysis. Extension of this catalytic methodology to other π-electrophiles is currently under investigation.[30]

Experimental Section

Catalytic conjugate addition of α-hydroxy ketones to nitroalkenes. (**Method A, benzylic ketols**) To a mixture of the corresponding benzylic ketol **1**–**4** (1 eq., 0.1 mmol) and nitroalkene **5** (2.0 eq., 0.2 mmol for aromatic nitroalkenes; 3.0 eq., 0.3 mmol for aliphatic nitroalkenes), in dichloromethane (0.3 mL) at room temperature (or cooled to the corresponding temperature), catalyst **C1**–**C6** (10 mol %) was added. The resulting suspension was stirred at the same temperature, until consumption of the α-hydroxy ketone as monitored by ^{1}H NMR. The mixture was quenched with HCl 2M (1 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The residue was subjected to flash column chromatography on silica gel (eluent Hexane/AcOEt 95:5 to 90:10). (**Method B, allylic ketols**) To a solution of the corresponding allylic ketol **16**–**18** (0.2 mmol, 1 equiv.) and nitroalkene **5** (0.22 mmol, 1.1 equiv.), in dichloromethane (0.4 mL), catalyst **C5** (6 mg, 0.01 mol, 5 mol %) was added at room temperature or –20 °C and the resulting mixture was stirred at that temperature until reaction completion (2–20 h, TLC). Then the reaction mixture was submitted to flash column chromatography (eluent hexane/ethyl acetate 90:10). The same procedure was employed for the reactions involving catalyst **C6**, but with a molar ratio of ketone/**5**/catalyst of 1.5:1:0.1.

Representative examples: **Compound 9Aa** (2-Benzyl-2-hydroxy-6-nitro-4-(4-nitrophenyl)-1,5-diphenylhexan-3-one): prepared from 3-benzyl-3-hydroxy-1-(4-nitrophenyl)-4-phenylbutan-2-one (**4A**) (37.5 mg, 0.1 mmol) and nitrostyrene (**5a**) (29.8 mg, 0.2 mmol) according to the general procedure using catalyst **C6**. White solid, yield: 51.9 mg, 0. 099 mmol, 99%. $[\alpha]_D^{25}$= –97.0° (c= 0.54, 99% *ee*, CH_2Cl_2). m.p. 187–188 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.86 (d, *J*= 8.7 Hz, 2H), 7.42–7.24 (m, 8H), 7.16 (d, *J*= 9.3 Hz, 2H), 7.00–6.88 (m, 3H), 6.86–6.75 (m, 2H), 6.58 (d, *J*= 7.1 Hz, 2H), 5.00 (d, *J*= 11.0 Hz, 1H), 4.43 (dd, *J*= 12.0, 10.3 Hz, 1H), 4.28 (dd, *J*= 11.0, 4.0 Hz, 1H), 4.17 (dd, *J*= 12.1, 4.0 Hz, 1H), 3.01 (d, *J*= 13.5 Hz, 1H), 2.27 (dd, *J*= 28.1, 13.6 Hz, 2H), 1.95 (d, *J*= 13.7 Hz, 1H), 1.75 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 208.9, 147.2, 139.9, 137.4, 134.6, 134.2, 130.8, 130.1, 129.8, 129.1, 128.8, 128.5, 128.5, 128.1, 127.3, 126.5, 124.0, 83.4, 78.1, 55.5, 46.2, 42.8, 42.4. UPLC-DAD-QTOF: $C_{31}H_{27}N_2O_6$ $[M–H]^-$ calcd.: 523.1869, found: 523.1880. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IA, hexane/isopropanol 90:10, flow rate= 1.0 mL/min, retention times: 16.7 min (major) and 22.7 min (minor)). **Compound 21a** (2-hydroxy-2-methyl-4-(2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one): prepared from 2-hydroxy-2-methyl-6-phenylhex-5-en-3-one **18** (40.8 mg, 0.2 mmol) and nitrostyrene (**5a**, 32.8 mg, 0.22 mmol) using **C5**. White solid, yield: 60 mg, 85%. $[\alpha]_D^{25}$= –60.3° (c= 1, 97% *ee*, CH_2Cl_2). m.p. 143–145 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ: δ 7.48–7.24 (m, 10H), 6.73 (d, *J*= 15.9 Hz, 1H), 6.10 (dd, *J*= 15.9, 9.5 Hz, 1H), 4.95–4.69 (m, 2H), 4.37–4.11 (m, 2H), 1.08 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.6, 128.9, 128.8, 128.6,

128.3, 126.5, 124.3, 78.0, 54.5, 45.7, 26.1, 25.9. UPLC-DAD-QTOF: $C_{21}H_{23}NO_4$ $[M+H]^+$ calcd.: 354.1705, found: 354.1707. The enantiomeric purity of the major diastereomer was determined by HPLC analysis (Daicel Chiralpak IB, hexane/isopropanol 90:10, flow rate= 1.0 mL/min, retention times: 17.6 min (minor) and 27.1 min (major)).

Hydrogenation of 21a to obtain 26: To a solution of (*S*,*E*)-2-hydroxy-2-methyl-4-((*S*)-2-nitro-1-phenylethyl)-6-phenylhex-5-en-3-one **21a** (206.6 mg, 0.58 mmol) in dry EtOAc (20 mL), Pd/C (10% w/w) was added (21 mg). Air was evacuated by applying vacuum and H_2 was introduced, repeating this process two additional times. The reaction mixture was stirred under H_2 atmosphere at room temperature for 1 h. Then, the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford compound **26** as a solid. Yield: 196 mg (95%). $[\alpha]_D^{25}$= +5.53° (c= 0.32, 94% *ee*, CH_2Cl_2). m.p. 94–96 ºC. ^{1}H NMR (300 MHz, ($CDCl_3$), δ: 7.41–7.19 (m, 8H), 7.14–7.06 (m, 2H), 4.90–4.76 (m, 2H), 4.09–4.01 (m, 1H), 3.70–3.64 (m, 1H), 2.64–2.39 (m, 2H), 2.12–1.97 (m, 1H), 1.96–1.81 (m, 1H), 1.30 (s, 1H), 1.25 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD), δ: 215.3, 140.6, 138.0, 129.0, 128.6, 128.1, 128.0, 128.0, 126.3, 75.9, 48.7, 44.2, 33.2, 29.8, 26.6. UPLC-DAD-QTOF: $C_{21}H_{25}NO_4Na$ $[M+Na]^+$ calcd.: 378.1681, found: 378.1686.

Scission of 26 to give 28: BH_3•THF complex (1 M, 1.5 mL, 1.5 mmol) was added to a solution of α-hydroxy ketone **26** (178 mg, 0.5 mmol) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at room temperature for 24 h. Then MeOH (2.5 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue was submitted to oxidation as follow. A suspension of sodium periodate ($NaIO_4$, 535 mg, 2.5 mmol) in water (1.25 mL) was added to a solution of the obtained diol (0.5 mmol) in methanol (2.5 mL). The mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. Water (4.5 ml) was added to the crude product and the resulting mixture was extracted with Et_2O (3 × 6 mL) and CH_2Cl_2 (2 × 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1) to afford a colorless oil. Yield of **28**: 110 mg (74%). ^{1}H NMR (400 MHz, ($CDCl_3$), δ: 9.54 (d, *J*= 2.8 Hz, 1H), 7.36–7.14 (m, 10H), 4.80 (dd, *J*= 6.8, 13.2 Hz, 1H), 4.76 (dd, *J*= 8.4, 13.2 Hz, 1H), 3.85 (dt, *J*= 6.8, 8.4 Hz, 1H), 2.75–2.60 (m, 1H), 2.64–2.39 (m, 3H), 2.06 (m, 1H), 1.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 202.9, 140.3, 136.0, 135.9, 129.2, 128.7, 128.3, 128.2, 126.5, 77.7, 52.7, 44.5, 33.2, 29.2. UPLC-DAD-QTOF: $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ calcd.: 320.1263, found: 320.1272.

Michael-aldol domino reaction involving 28 and acrolein to give cycloadducts 29 and 30: DIPEA (10.2 μL, 0.06 mmol) was added to a solution of aldehyde **28** (59.4 mg, 0.2 mmol) and acrolein (26.6 μL, 0.4 mmol) in CH_2Cl_2 (0.8 mL) and the solution was stirred overnight at room temperature. CH_2Cl_2 (5 mL) was added and the mixture was washed with 1 M HCl (5 mL). The organic extract was dried over $MgSO_4$, filtered and the solvent was evaporated to afford the corresponding dialdehyde. ^{1}H NMR (400 MHz, ($CDCl_3$), δ: 9.68 (s, 1H), 9.61 (d, *J*= 2.4 Hz, 1H), 7.40–7.13 (m, 10H), 5.28 (m, 1H), 3.52 (dd, *J*= 5.6, 10.4 Hz, 1H), 2.65 (m, 2H), 2.53 (m, 1H), 2.48 (t, *J*= 6.8 Hz, 2H), 1.94 (m, 1H), 1.90 (t, *J*= 6.8 Hz, 2H), 1.74 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 203.0, 199.3, 140.5, 134.4, 129.3, 129.2, 128,6, 128,5, 128,4, 126.4, 88.8, 51.6, 51.0, 39.5, 33.3, 29.6, 24.4. L-Proline (2.1 mg, 0.02 mmol) was added to a solution of the above obtained dialdehyde in THF (0.4 mL) at 0 °C and the mixture was stirred at the same temperature for 8 h. CH_2Cl_2 (5 mL) was added and the mixture was washed with water (2 × 5 mL). The organic extract was dried over $MgSO_4$, filtered and the solvent was evaporated to afford a mixture of cyclohexanecarbaldehyde epimers **29** and **30** in a 90:10 ratio. Combined yield: 49.5 mg (70%, two steps). Each isomer was separated by a quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 1:1) and stored at –30 °C. Major isomer ((1*S*,2*R*,3*S*,4*S*,5*S*)-2-hydroxy-5-nitro-3-phenethyl-4-phenylcyclohexanecarbaldehyde **29**): ^{1}H NMR (400 MHz, ($CDCl_3$), δ: 10.04 (s, 1H), 7.35–6.98 (m, 10H), 4.91 (dt, *J*= 6.0, 11.6 Hz, 1H), 4.50 (dd, *J*= 6.0, 10.8 Hz, 1H), 4.00 (t, *J*= 5.6 Hz, 1H), 3.36 (dt, *J*= 4.4, 5.6 Hz, 1H), 2.67 (m, 1H), 2.60 (m, 2H), 2.50 (m, 1H), 2.15–2.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 204.5, 141.4, 134.3, 130.4, 128.8, 128.6, 128.4, 128.2, 126.0, 82.8, 70.1, 50.2, 47.7, 44.2, 33.0, 30.5, 23.1. UPLC-DAD-QTOF: $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ calcd.: 376.1525, found: 376.1527. Minor isomer (**30**): ^{1}H NMR (400 MHz, ($CDCl_3$), δ: 9.92 (s, 1H), 7.36–7.00 (m, 10H), 4.83 (ddd, *J*= 4.4, 5.6, 12.0 Hz, 1H), 4.33 (t, *J*= 10.4 Hz, 1H), 4.06 (t, *J*= 5.6 Hz, 1H), 2.70–2.66 (m, 1H), 2.57–2.38 (m, 4H), 2.17 (m, 1H), 2.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ: 202.7, 141.4, 133.6, 130.6, 128.9, 128.4, 128.3, 128.2, 126.0, 85.6, 68.8, 54.2, 47.9, 45.5, 32.8, 30.2, 23.0. UPLC-DAD-QTOF: $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ calcd.: 376.1525, found: 376.1527.

Synthesis of 31 (sequential double Michael/reduction of **18**): To a solution of the corresponding hydroxy ketone **18** (40.9 mg, 0.2 mmol, 1 equiv.) and *trans*-β-nitrostyrene (89.5 mg, 0.6 mmol, 3 equiv.) in dichloromethane (0.4 ml), catalyst **C6** (23.8 mg, 0.04 mmol, 20 mol%) was added at room temperature and the resulting mixture was stirred to completion of the reaction (5 days). Then the reaction mixture was submitted to flash column chromatography (hexane/ethyl acetate 90:10). The residue was dissolved in dry EtOAc (40 ml) and Pd/C (Pd 10% in activated carbon) was added (10.1 mg). The air was evacuated by vacuum and H_2 was introduced (this process was carried out three times). The reaction mixture was stirred under H_2 atmosphere at room temperature for 2 h. Then, the mixture was filtered over celite and the filtrate was concentrated under reduced pressure to afford product **31** as an oil. Yield: 70.6 mg (70%). $[\alpha]_D^{24}$ = +13,9º (*c*= 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.05 (m, 15H), 5.49 (dd, *J*= 11.2, 3.6 Hz, 1H), 5.02 (dd, *J*= 14.0, 11.2 Hz, 1H), 4.88 (dd, *J*= 14.0, 3.6 Hz, 1H), 3.93 (dd, *J*= 11.2, 5.2 Hz, 1H), 3.84 (dt, *J*= 10.8, 3.4 Hz, 1H), 3.71–3.67 (m, 1H), 3.00 (sb, 1H), 2.56–2.42 (m, 2H), 2.23–2.12 (m, 1H), 1.87–1.75 (m, 1H), 1.22 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.8, 141.0, 136.3, 135.1, 129.5, 129.4, 128.9, 128.7, 128.5, 128.4, 127.2, 126.2, 93.0, 73.5, 48.9, 47.8, 43.9, 33.3, 30.4, 28.1, 27.1. UPLC-DAD-QTOF: $C_{29}H_{36}N_3O_6$. $[M+NH_4]^+$ calcd.: 522.2604, found: 522.2611.

Sequential reduction/oxidative cleavage of 31 to give 32: BH_3•THF complex (1 M, 1.5 mL, 1.5 mmol) was added to a solution of α-hydroxy ketone **31** (252 mg, 0.5 mmol) in dry THF (1.5 mL) at 0 °C and the resulting solution was stirred at room temperature for 24 h. Then MeOH (2.5 mL) was added and the resulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the resulting diol product was subjected to oxidative scission by treatment with $NaIO_4$. A suspension of sodium periodate $NaIO_4$ (535 mg, 2.5 mmol) in water (1.25 mL) was added to a solution of the diol (0.5 mmol) in methanol (2.5 mL). The mixture was stirred overnight at room temperature. Then the solvent was removed under reduced pressure. Water (4.5 ml) was added to the crude product and the resulting mixture was extracted with Et_2O (3 × 6 mL) and CH_2Cl_2 (2 × 6 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated. The crude material was purified by flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1) to afford the tittle product as a colorless oil. Yield: 179 mg (80%). $[\alpha]_D^{23}$ = +16.4º (*c*= 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.58 (dd, *J*= 2.0, 0.8 Hz, 1H), 7.49–6.98 (m, 15H), 5.62 (dd, *J*= 11.6, 3.6 Hz, 1H), 5.02 (dd, *J*= 14.0, 11.0 Hz, 1H), 4.83 (dd, *J*= 4.2 Hz, 1H), 2.74–2.60 (m, 2H), 2.47–2.42 (m, 1H), 2.01–1.92 (m, 1H), 1.75–1.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 140.2, 134.9, 133.3, 129.9, 129.5, 129.3, 129.2, 129.0, 128.7, 128.4, 127.1, 126.5, 92.9, 73.6, 51.2, 49.3, 43.5, 33.5, 29.7. UPLC-DAD-QTOF: $C_{26}H_{26}N_2NaO_5$. $[M+Na]^+$ calcd.: 469.1739, found 469.1730.

Conversion of 32 into 33 and 34 (intramolecular Henry reaction of **32**): DIPEA (3.5 μL, 0.02 mmol) was added to a solution of aldehyde **32** (44.6 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) at 0 °C and the resulting mixture was stirred at room temperature for 20 h. CH_2Cl_2 (5 mL) was added and the mixture was washed with 1M HCl (5 mL). The organic extract was dried over $MgSO_4$, filtered and the solvent was evaporated to afford a mixture of epimeric cyclohexanols **33** and **34** in a 92:8 ratio. The major isomer **33** was separated as a white solid by a quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1). Yield: 37 mg (82%). m.p.= 191–193 ºC. $[\alpha]_D^{25}$ = –38.3º (c= 0.65, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.05 (m, 15H), 6.17 (dd, *J*= 12.6, 2.2 Hz, 1H), 5.26 (t, *J*= 5.2 Hz, 1H), 4.74 (t, *J*= 2.4 Hz, 1H), 4.42 (dd, *J*= 12.4, 5.2 Hz, 1H), 4.03 (t, *J*= 5.2 Hz, 1H), 2.81–2.74 (m, 1H), 2.56–2.48 (m, 1H), 2.47–2.42 (m, 1H), 2.22–2.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.5, 136.3, 133.8, 129.3, 129.0, 128.8, 128.5, 128.4, 128.3, 127.9, 127.2, 126.2, 91.6, 83.5, 71.1, 45.4, 42.4, 42.1, 35.4, 27.6. UPLC-DAD-QTOF: $C_{26}H_{30}N_3O_5$. $[M+NH_4]^+$ calcd.: 464.2185, found 464.2190.

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Keywords: asymmetric organocatalysis • ester equivalents • Brønsted bases • conjugate additions • hydroxy ketones

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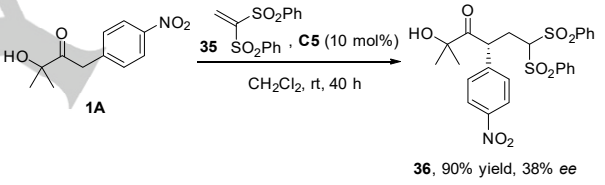

36, 90% yield, 38% *ee*

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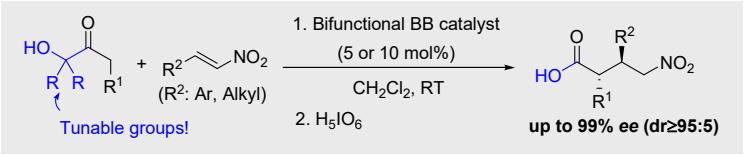

Direct with a little help: The direct, asymmetric α-functionalization of esters and related carboxylic acid derivatives, a challenge because of intrinsically difficult enolization, is tackled by using α-hydroxy ketones as enolization-prone, tunable carboxylic acid equivalents. These templates in the presence of chiral bifunctional Brønsted base catalysts react smoothly and in highly stereoselective manner with nitroalkenes, including the recalcitrant aliphatic nitroalkenes.

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α-Hydroxy Ketones as Masked Ester Donors in Brønsted Base-Catalyzed Conjugate Additions to Nitroalkenes