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

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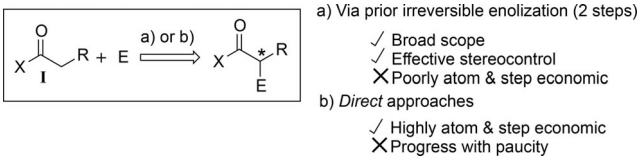
Abstract: The catalyst-controlled enantioselective direct addition reaction of enolizable esters and related carboxylic acid derivatives to π electrophiles remains a difficult synthetic transformation. In this study, the suitability of α-hydroxy ketones as ester equivalents capable of being activated 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 (diastereomeric ratio (d.r.) ≥95:5, up to 99% enantiomeric excess (*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 1 a).[1] In contrast, direct protocols (that is, without a separate enolization process and consumption of stoichiometric base) involving enolizable esters, amides, or similar and a chiral catalyst are less developed (Scheme 1 b). 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 N-heterocyclic carbene (NHC) and isothiourea catalysts has also been reported to afford mainly lactone- and lactam-type cyclic products.[7] In addition, few 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 diastereo- and enantioselectivity of the reaction is still a challenge.



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

Although all of these studies deal with enolizable substrates of type **I** (Scheme 1; 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 2 a). 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 easy to modify to access the corresponding ketone and aldehyde products as well. However, and despite its potential and practicality, to the best of our knowledge, no direct version of this approach, relying on a combination of an achiral α-hydroxy ketone and a suitable chiral catalyst, has been reported so far. Herein, 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

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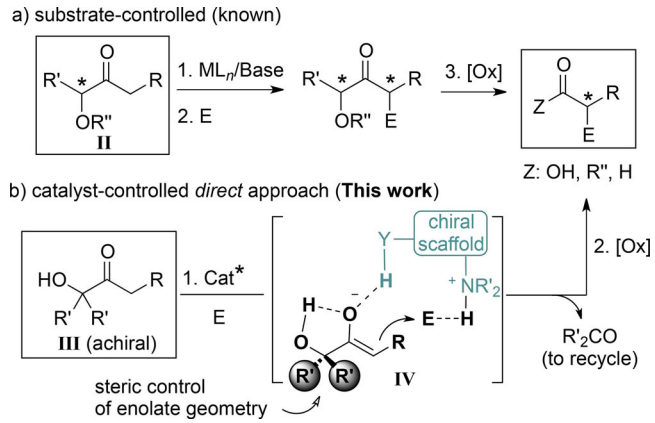


Scheme 2. α-Hydroxy ketones as donor carboxylic acid equivalents.

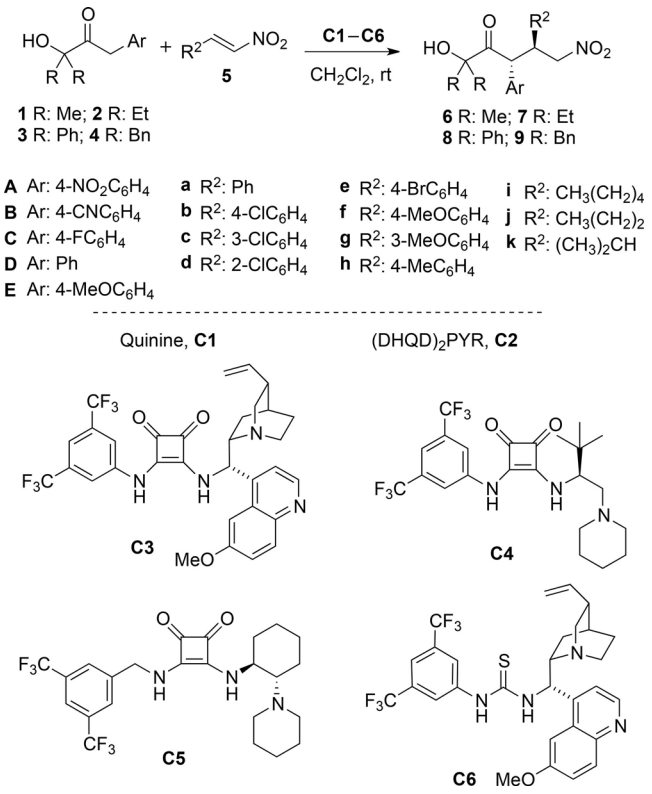
adducts in high stereoselectivity. This constitutes the first demonstration of achiral α-hydroxy ketones as ester and aldehyde donor equivalents in the context of asymmetric catalysis.[13]

Results and Discussion

The underlying idea is that substrate **III** may be activated by a bifunctional tertiary amine/hydrogen-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 **1A** with **5a** was selected and several Brønsted bases were screened (Scheme 3).

As shown by the results in Table 1, both **C1** and **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 (Table 1, entries 1 and 2). Among several bifunctional catalysts examined, squaramide **C3**[14] provided the addition adduct **6Aa** in nearly quantitative yield after 5 h at room temperature, but with as-yet unsatisfactory selectivity (Table 1, entry 3). Catalysts **C4**[15] and **C5** behaved similarly, both affording slightly better enantiocontrol (70 and 69% *ee*, respectively; Table 1, entries 4 and 5). Finally, thiourea catalyst **C6**[16] proved to be superior in this reaction to afford a product with 80% *ee* (Table 1, entry 6). Then, the influence of the two R groups at Cα of the ketol substrate, which can be readily prepared through the method reported by Qi et al. from the corresponding alkyne, CO_2, and simple ketones as starting materials,[17] was examined. Upon moving from **1A** (R = Me) to **2A** (R = Et) and **3A** (R = Ph), there is not much impact on the reaction selectivity (compare Table 1, entries 3–5 with 6–8 and 9). However, the reaction employing **4A** (R = Bn) led to an outstanding 99% *ee* with either catalyst **C3** or **C6** (Table 1, entries 10 and 12). Notably, in all of the above experiments, essentially a single diastereomer was observed by ^{1}H NMR spectroscopy (d.r. ≥ 95:5).

Based on the above results, ketone **4A** and catalyst **C6** were selected for exploring the scope of the reaction with regard to the nitroalkene component. As shown from the data in Table 2, several β-aryl-substituted nitroalkenes, including electron-poor (Table 2, entries 1–4) and -rich (Table 2, entries 5–7) systems, participate in the reaction with **4A** to afford the corresponding products **9A** in good yields and essentially perfect stereocontrol (d.r. ≥ 95:5, 99% *ee*) in all cases. Importantly, the



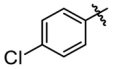
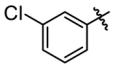
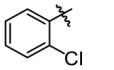
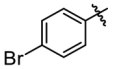
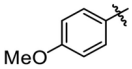
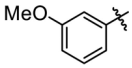
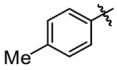
Scheme 3. Conjugate addition of α-hydroxy ketones to nitroalkenes catalyzed by Brønsted bases **C1**–**C6**. Bn = benzyl, $(DHQD)_2PYR$ = hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether.

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

Entry	Reaction	Catalyst	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1		**C1**	72	97	10[d]
2		**C2**	72	86	−50[d]
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[d]
6		**C3**	24	97	76
7	**2A** + **5a** → **7Aa** (cat; R: Et)	**C4**	48	55[e]	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[e]	88
12		**C6**	24	99	99

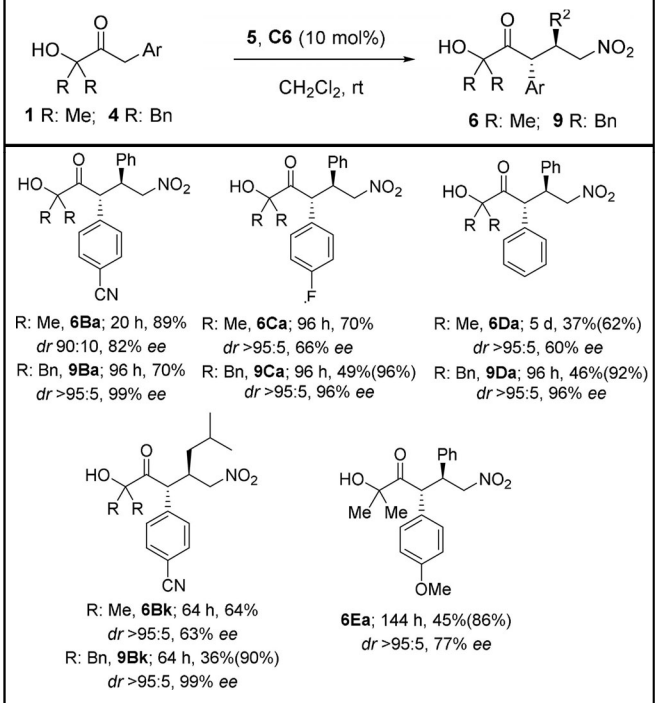
[a] Reactions conducted on a 0.1 mmol scale in CH_2Cl_2 (0.3 mL; 1:2:0.1 molar ratio of ketone/**5a**/catalyst); diastereomeric ratio (d.r.) > 95:5 in all entries was determined by ^{1}H NMR spectroscopy (300 MHz) analysis of the crude sample. [b] Yields of products isolated after chromatography. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [d] The reaction was performed at −20 °C. [e] Conversion; yield not determined.

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

Entry	Nitroalkene	R^2	Product	*t* [h]	Yield[b] [%]	d.r.[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 CH_2Cl_2 (0.3 mL; molar ratio of **4A**/**5**/catalyst, for R^2 = aromatic, 1:2:0.1; for R^2 = aliphatic, 1:3:0.2) at RT, unless otherwise stated. [b] Yields of products isolated after chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis by using a chiral stationary phase. [e] Yield in parenthesis based on recovered starting material.

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



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

more challenging alkyl-substituted nitroalkenes, such as **5i** and **5j**, were also competent reaction partners that afforded the corresponding adducts **9Ai** and **9Aj** in 75 and 76% yield, diastereomeric ratios of ≥95:5, and *ee* values of 96 and 99%, respectively. In these instances, longer times were required for useful conversion. With the more demanding isopropyl nitroalkene **5k**, reactivity was an issue, but selectivity remained still high (90:10 d.r., 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 shown by the data in Table 3, the reaction tolerates electron-poor, neutral, or electron-rich aryl substituents. However, in the last case, the reaction proceeded very slowly. For instance, the reaction of **5a** and **4B**, with a *p*-cyanophenyl group at Cα′, proceeded to completion in about 96 h to afford adduct **9Ba** in good yield as essentially a single isomer. Reactions of the *p*-fluorophenyl and phenyl analogues **4C** and **4D**, respectively, were incomplete after 96 h (isolated in yields of 49 and 46%, respectively), although selectivity remained high in both cases (>95:5 d.r.; 96% *ee*). The reaction of **4E** was impractical; however, the *gem*-dimethyl analogue **1E** could react with **5a** to afford adduct **6Ea** as a 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; sterically more demanding α,α-dibenzyl ketols **4** require longer reaction times than those of α,α-dimethyl congeners **1**, but lead to considerably better diastereo- (d.r. ≥95:5) and enantioselectivities (96–99% *ee*). Importantly, high selectivity was also attained in the reaction of **4B** with **5k** to afford adduct **9Bk** as a single diastereomer and 99% *ee*. The absolute configuration of adduct **9Ab** was established by single-crystal X-ray structure analysis,[18] and those of the remaining adducts by analogy and by assuming a uniform reaction mechanism.

Based on the most accepted transition-state 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 template **1A** is apparent if reaction conversions are compared with those obtained with derivative **1A**′. As shown by control experiments in Figure 1b, although the **C6**-catalyzed reaction of **5a** with **1A** to produce **6Aa** is essentially over after 10 h at room temperature, the reaction involving **1A**′ progresses much more slowly, with around 50% conversion reached after 20 h. The same trend was observed for the reaction of the O-TMS derivative of **1B**.[20]

Additional control experiments with the related (thio)esters and aldehydes (Scheme 4) as the donor component further demonstrated the importance of the α-hydroxy ketone template in this development. For example, methyl *p*-nitrophenylacetate did not react at all with **5a** in dichloromethane in the presence of catalyst **C6** (10 mol%).[21] More reactive thioester **10** barely reacted under the same conditions to reach a maximum conversion of 55% after 96 h,[8c,d] which gives rise to

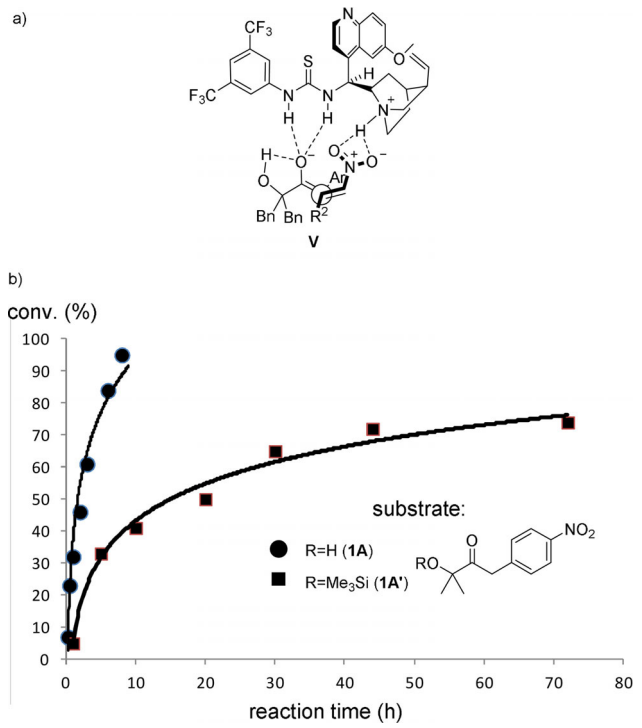
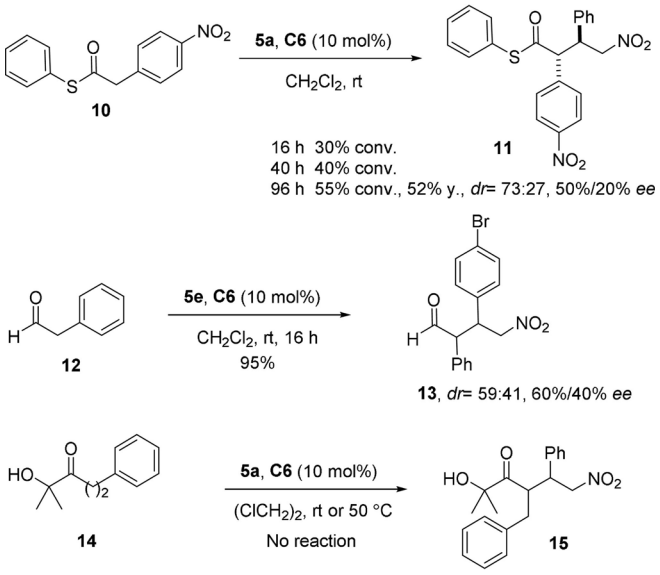


Figure 1. a) Structure of the proposed stereomodel. b) Progress of the **C6**-catalyzed reaction of **5a** with **1A** and trimethylsilyl (TMS) derivative **1A′**.



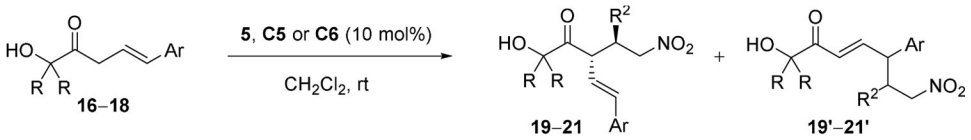
Scheme 4. Unsuitable ketone and thioester substrates.

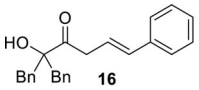
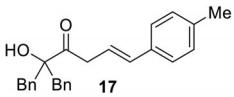
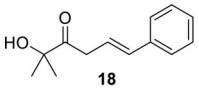
product **11** with poor selectivity. As expected, reactivity was not a problem with phenylacetaldehyde (**12**), but the resulting aldehyde **13** was configurationally unstable and an almost equimolar mixture of epimers was isolated. One limitation of the method is the unsuitability of α-hydroxy ketones with decreasing α′-carbon acidity, such as **14**, which remains intact after 24 h under the above catalytic conditions (or even at 50 °C). In this respect, we recently found that related β′,γ′-unsaturated ketols, which upon enolization would form a vinylogous enolate, were competent substrates for this reaction with nitroolefins.[22] Additionally, 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 types of ketol substructures were optimum with respect to both reactivity and selectivity. As shown by the results in Table 4, the catalyzed reaction of ketones **16** and **17** with **5a** proceeded virtually to completion within a few hours at room temperature to afford the corresponding Michael adducts **19** and **20**, although accompanied by 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**, although both provided high levels of diastereo- and enantiocontrol (essentially a single stereoisomer was isolated). However, neither catalyst was able to control the α- versus γ-regioselectivity properly (product ratios from 41:59 to 74:26, at best). Experiments with the parent *gem*-dimethyl ketone **18** instead demonstrated once again that this regioselectivity issue could be properly addressed. With this ketol substrate, and catalyst **C6**, mixtures of the corresponding α- and γ-adducts **21**/**21′** were obtained again (Table 4, entries 6, 8, 10, and 12). However, with catalyst **C5**, the corresponding adduct **21** could be obtained exclusively. For instance, for the reaction of **18** with **5a**, product **21a** was isolated in 85% yield, as essentially a single diastereomer and with 97% *ee* (Table 4, entry 5). This pattern was reproduced with **5b**, **5c**, **5f**, and **5i**, giving rise to the corresponding adducts **21** as clean products, which were isolated in high yields, with essentially perfect diastereoselectivity and 94–98% *ee* (Table 4, entries 7, 9, 11, and 13).

Adducts obtained through the above catalytic reactions may serve as versatile platforms in synthesis. For instance, the oxidative cleavage of the ketol moiety in **9Aa** by treatment with H_5IO_6 afforded the arylacetic acid **22** in 89% yield (Scheme 5), along with dibenzyl ketone as the only organic side product, which could be recovered and reused.[23] Compound **22** was then transformed into **11** under standard conditions. Thus, the lack of reactivity and selectivity associated with simple arylacetic esters and thioesters may be circumvented by using α-hydroxy ketones as donor ester equivalents. Alternatively, the 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 two steps. It should be noted that in no case was epimerization at the α-carbon observed; an important feature of the present approach, upon considering the high tendency of these compounds (i.e., arylacetic aldehydes, see above) towards base-promoted isomerization. On the other hand, the C–NO_2 group in **9Aa** could be oxidized under Mioskowski conditions,[24] without affecting the ketol moiety, to deliver carboxylic acid **23**. The first oxidation run was incomplete (36%), but, by applying further oxidation runs to the recovered unoxidized material, product **23** was isolated in a combined yield of 71%.

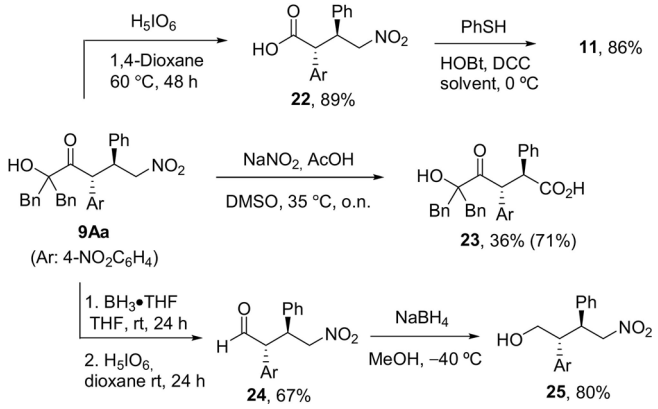
One particular advantage of the high regio- and stereoselectivity observed in the reactions with β′,γ′-unsaturated ketols is that a simple hydrogenation of the C=C bond in the resulting

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

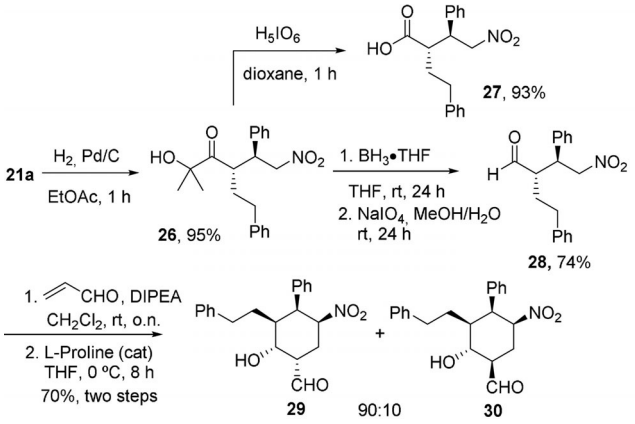


Entry[b]	Ketol substrate	Nitroalkene R^2	Product	Cat.	T [°C]	t [h]	Ratio α/γ	Yield [%][c]	d.r.[d]	*ee* [%][e]
1		**5a**, Ph	**19**/**19′**	**C5**	20	2	72:28	63	>95:5/>95:5	>98/84
2				**C6**	20	2	41:59	35	>95:5/>95:5	>98/94
3		**5a**, Ph	**20**/**20′**	**C5**	20	2	74:26	70	>95:5/>95:5	98/>98
4				**C6**	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				**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/–

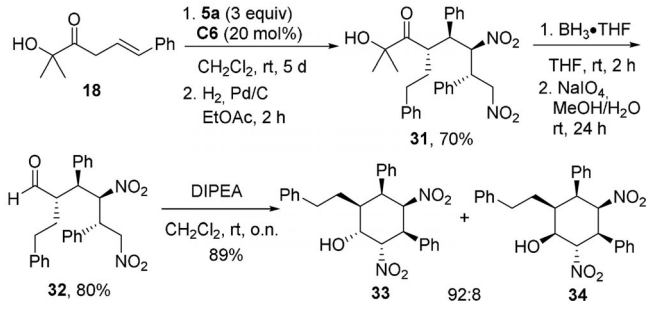
[a] Reactions conducted on **16**–**18** (0.2 mmol) in CH_2Cl_2 (0.3 mL) at RT, unless otherwise stated. Molar ratios of **16**–**18**/**5**/catalyst: 1.5:1:0.1 (for **C6**) or 1:1.1:0.05 (for **C5**). [b] For entries 5, 7, and 11, see ref. [22]. [c] Yields of isomers **19**–**21** isolated after chromatography. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis by using a chiral stationary phase. ND: not determined.



Scheme 5. Scission of ketol and nitro moieties of the adducts. HOBt = 1-hydroxybenzotriazole, DCC = *N*,*N*′-dicyclohexylcarbodiimide.



adducts (e.g., **21a**; Scheme 6) gives access to compounds such as **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** in hand, a suitable Michael/aldol domino process,[25,26] involving acrolein as a reaction partner, allowed the fully enantiocontrolled construction of densely substituted cyclohexanecarbaldehydes **29** and **30** in 70% combined yield and a 90:10 ratio.[27] This ratio was temperature-dependent and, if 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



Scheme 6. Further possibilities for the elaboration of adducts. DIPEA = *N*,*N*-diisopropylethylamine.

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 to 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 ratio of 92:8 and combined yield of 89%.[26g] The configurations of cyclic products **29/30** and **33/34** were preliminary established through the correlation of the H–H coupling constants in their ^{1}H NMR spectra, and then confirmed by single-crystal X-ray analysis of **33**.[20]

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,[26g,27] which proceeded via the corresponding aldehydes with relative α/β *syn* configuration instead.

Conclusion

Enolizable α-hydroxy α,α-disubstituted ketones were introduced as efficient ester and aldehyde donor equivalents in asymmetric catalysis. The reactivity and stereoselectivity profile of these templates could be easily modulated by varying the size of the *gem*-R substituents at Cα; the α,α-dibenzyl-substituted congeners provided the best enantiocontrol with the selected reaction and catalysts. Specifically, the conjugate addition reaction to nitroalkenes, including challenging β-alkyl-substituted nitroalkenes, proceeded smoothly under bifunctional Brønsted base catalysis to afford adducts with very high diastereo- and enantioselectivity (d.r. ≥95:5, up to 99% *ee*). Elaboration of the resulting adducts through smooth oxidative ketol cleavage gave access to the corresponding enantioenriched α-branched carboxylic acid and aldehyde products, including aryl acetics,[28] and dibenzylacetone byproduct, which could be separated and recycled. Additional reaction sequences were also applicable to construct densely functionalized carbocycles with complementary relative configuration, compared with previous methods based on enamine catalysis. Extension of this catalytic methodology to other π electrophiles is currently under investigation.[29]

Experimental Section

Catalytic conjugate addition of α-hydroxy ketones to nitroalkenes

Method A: Benzylic ketols: Catalyst **C1**–**C6** (10 mol%) was added to a mixture of the corresponding benzylic ketol **1**–**4** (1 equiv, 0.1 mmol) and nitroalkene **5** (2.0 equiv, 0.2 mmol for aromatic nitroalkenes; 3.0 equiv, 0.3 mmol for aliphatic nitroalkenes), in dichloromethane (0.3 mL) at room temperature (or cooled to the corresponding temperature). The resulting suspension was stirred at the same temperature, until consumption of the α-hydroxy ketone, as monitored by ^{1}H NMR spectroscopy. The mixture was quenched with 2 M HCl (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: Catalyst **C5** (6 mg, 0.01 mol, 5 mol%) was added at room temperature or −20 °C 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), and the resulting mixture was stirred at that temperature until completion of the reaction (2–20 h, as determined by 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: Compound **9Aa** was prepared from **4A** (37.5 mg, 0.1 mmol) and **5a** (29.8 mg, 0.2 mmol), according to the general procedure, with catalyst **C6**. White solid; yield: 51.9 mg, 0.099 mmol, 99%; $[\alpha]_D^{25} = -97.0^\circ$ ($c = 0.54$, 99% *ee*, CH_2Cl_2); m.p. 187–188 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (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 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.9$, 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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{31}H_{27}N_2O_6$ $[M-H]^-$: 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^{-1}, retention times: 16.7 (major) and 22.7 min (minor)).

Compound 21a: Compound **21a** was prepared from **18** (40.8 mg, 0.2 mmol) and **5a** (32.8 mg, 0.22 mmol) with **C5**. White solid; yield: 60 mg, 85%; $[\alpha]_D^{25} = -60.3^\circ$ ($c = 1$, 97% *ee*, CH_2Cl_2); m.p. 143–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–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 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.6$, 128.9, 128.8, 128.6, 128.3, 126.5, 124.3, 78.0, 54.5, 45.7, 26.1, 25.9 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4$ $[M+H]^+$: 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^{-1}, retention times: 17.6 (minor) and 27.1 min (major)).

Hydrogenation of 21a to obtain 26: Pd/C (10% w/w) was added (21 mg) to a solution of **21a** (206.6 mg, 0.58 mmol) in dry EtOAc (20 mL). Air was evacuated by applying vacuum and H_2 was introduced; this process was repeated two additional times. The reaction mixture was stirred under H_2 atmosphere at room temperature for 1 h. Then, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to afford **26** as a white solid (196 mg, 95%). $[\alpha]_D^{25} = +5.53^\circ$ ($c = 0.32$, 94% *ee*, CH_2Cl_2); m.p. 94–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.41$–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 ppm (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 215.3$, 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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{25}NO_4Na$ $[M+Na]^+$: 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 **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 re-

sulting mixture was stirred at room temperature for 30 min. The solvents were removed under reduced pressure and the residue was submitted to oxidation as follows. A suspension of $NaIO_4$ (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 **28** as a colorless oil (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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{18}H_{19}NO_3Na$ $[M+Na]^+$: 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 **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 ppm (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 ppm.

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 epimers **29** and **30** in a ratio of 90:10. Combined yield: 49.5 mg (70%, two steps). Each isomer was separated by quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 1:1) and stored at −30 °C. Major isomer (**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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$: 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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$: 376.1525; found: 376.1527.

Synthesis of 31 (sequential double Michael/reduction of 18): catalyst **C6** (23.8 mg, 0.04 mmol, 20 mol%) was added at room temperature to a solution of **18** (40.9 mg, 0.2 mmol, 1 equiv) and **5a** (89.5 mg, 0.6 mmol, 3 equiv) in dichloromethane (0.4 mL), and the resulting mixture was stirred until 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 10% Pd/C was added (10.1 mg). Air was evacuated under 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 through Celite and the filtrate was concentrated under reduced pressure to afford **31** as an oil (70.6 mg, 70%). $[\alpha]_D^{24} = +13.9°$ (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 (br s, 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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{29}H_{36}N_3O_6$ $[M+NH_4]^+$: 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 **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 $NaIO_4$ (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 **32** as a colorless oil (179 mg, 80%). $[\alpha]_D^{23} = +16.4°$ (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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{26}H_{26}N_2NaO_5$ $[M+Na]^+$: 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 **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 1 M HCl (5 mL). The organic extract was dried over $MgSO_4$, filtered, and the solvent was evaporated to afford a mixture of epimeric **33** and **34** in a ratio of 92:8. Major isomer **33** was separated as a white solid by quick flash column chromatography on silica gel (eluent hexane/ethyl acetate 20:1). Yield: 37 mg (82%); m.p. 191–193 °C; $[\alpha]_D^{25} = -38.3°$ (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 ppm (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 ppm; UPLC-DAD-QTOF: *m/z* calcd for $C_{26}H_{30}N_3O_5$ $[M+NH_4]^+$: 464.2185; found: 464.2190.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: addition · asymmetric catalysis · esters · organocatalysis · synthesis design

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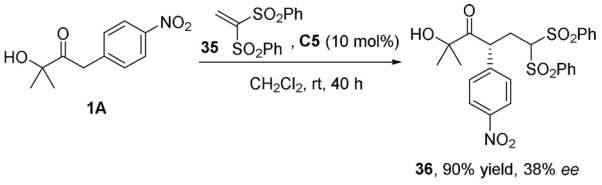

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FULL PAPER

Organocatalysis

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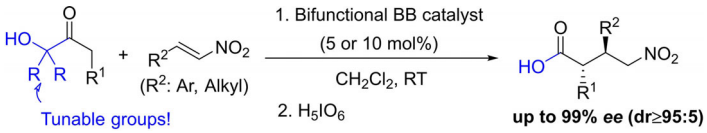
α-Hydroxy Ketones as Masked Ester Donors in Brønsted Base Catalyzed Conjugate Additions to Nitroalkenes



Head in the right direction: The direct, asymmetric α-functionalization of esters and related carboxylic acid derivatives is a challenge because of intrinsically difficult enolization. This problem is tackled by using α-hydroxy ketones as enolization-prone, tunable carboxylic acid equivalents. These templates react smoothly and in highly stereoselective manner with nitroalkenes in the presence of chiral bifunctional Brønsted base (BB) catalysts (see scheme).