Enantioselective Addition of Alkynyl Ketones to Nitroolefins Assisted by Brønsted Base/H-Bonding Catalysis

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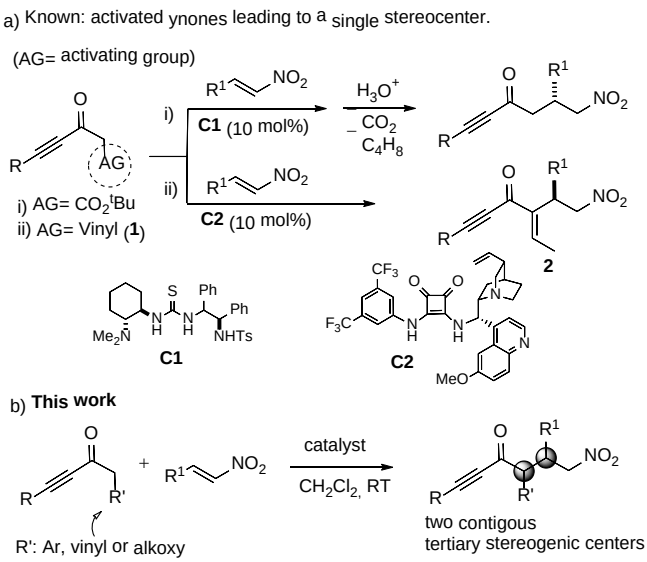
Abstract: Various sets of enolizable alkynyl ketones (including methyl ynones with α-aryl, α-alkenyl and α-alkoxy groups) are able to react smoothly with nitroolefins under the assistance of bifunctional Brønsted base/H-bond catalysts to provide adducts with two consecutive tertiary stereocenters in a highly diastereo- and enantioselective fashion. Further transformation of the obtained adducts into optically active acyclic and polycyclic molecules, including some with intricate carbon skeletons, is also demonstrated.

Introduction

Given the rich chemistry of both the carbon-carbon triple bond[1] and the carbonyl function,[2] alkynyl ketones (α,β-ynones) are excellent building-blocks for organic synthesis.[3] Therefore, the development of catalytic methods for the proliferation of simple ynones through new C–C bond forming processes into configurationally defined, structurally and functionally more complex, ynone molecules is highly desirable. One logical approach would rely on the α-functionalization of enolizable ynones with electrophiles, but the implementation of catalytic asymmetric methodologies progresses very slowly. One problem relies on the tendency of α,β-ynones to act as Michael acceptors rather than donors.[4] In addition, useful methods would require exquisite control of the intervening ketone enolate geometry as well as the stereochemistry of the subsequent C–C bond forming reaction. Some direct asymmetric aldol[5] and Mannich[6] reactions of enolizable ynones acting as donor components promoted by bifunctional metal catalysts[5a-e, 6] or enamine activation[5f-h] are known. In some instances, the enamine activation approach cannot stop at the acyclic addition adduct which undergoes intramolecular cyclization,[7] hence exemplifying the tendency of α,β-ynones to act as Michael acceptors.

As a complement to metal- and aminocatalytic activation strategies, Brønsted base catalysis bears great interest considering it proceeds under proton transfer conditions, with ideal atom economy and usually broad functional group tolerance.[8] However, a general problem with this type of activation is the functional pKa barrier of most catalysts that compromises their efficiency with less acidic carbon pronucleophiles.[9] To our knowledge there is a single report on asymmetric Brønsted base-catalyzed α-additions of enolizable ynones, by Peng, Wang and Shao (Scheme 1a, top).[10] Ynone substrates bearing an ester group at Cα are used, requiring a final decarboxylation by acid treatment at 110 ºC in toluene.



Scheme 1. Progress on bifunctional Brønsted base assisted direct Michael reactions of alkynyl ketones.

During recent studies on the catalyst-controlled reactivity of transiently generated vinylogous ketone enolates,[11] we found that alkynyl allyl ketones are a suitable subset of allyl ketones for their reaction with nitroolefins in the presence of bifunctional Brønsted base/H-bond catalysts like **C2**[12] (Scheme 1a down). Interestingly, these reactions proceeded with nearly perfect enantio- and α/γ-selectivity, but, unfortunately, the C=C double bond in adducts isomerizes spontaneously to the most stable α,β-position with loss of a stereocenter.[11] Therefore, both the above Brønsted base catalyzed methods afford products with a single new stereocenter. In the present investigation we demonstrate that the Brønsted base activation of enolizable α,β-ynones can be applied beyond the above constrains and thus becomes a practical approach to synthetically useful building-blocks. Specifically, ynones bearing an arylmethyl, alkoxymethyl or α-alkenyl sidearm all resulted suitable substrates for direct, Brønsted base-catalyzed Michael reactions producing adducts with two contiguous stereogenic centers in high selectivity (Scheme 1b). Details of the substrate scope, catalyst requirements and the utility of thus obtained adducts for

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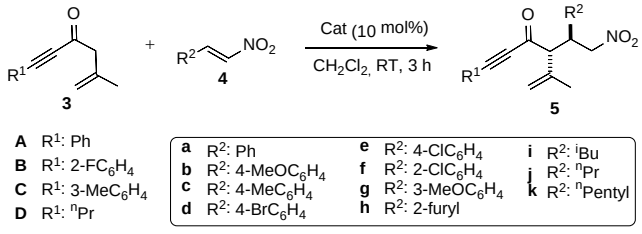
accessing stereochemically complex carbon skeletons, are shown.

Results and Discussion

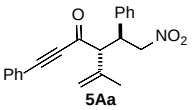
Alkenyl alkynyl ynones. Background and reaction generality. In our preliminary study allyl alkynyl ketones **1** were found to react with nitroolefins in the presence of catalyst **C2** to afford the Morita-Baylis-Hillmann type products **2**.[11] These observations indicate that the initially formed adduct isomerizes spontaneously, with one of the newly created stereocenters being ultimately loosed (Scheme 1a). Our first task was to check whether this isomerization bias is general for other allylic systems. The experiments involving 1,1-(*gem*)-disubstituted allylic ynone **3A** and nitrostyrene **4a** in the presence of several bifunctional Brønsted base catalysts[13] (Scheme 2 and Table 1) showed that, indeed, the β,γ-unsaturated adduct **5Aa** resists isomerization regardless the catalyst employed. For instance, after 3 h of stirring at room temperature with 10 mol% catalyst **C2**, adduct **5Aa** was obtained in 80% isolated yield and an excellent 98% *ee*, although a nearly equimolar mixture of diastereomers was produced (entry 1). With the N-benzyl analog **C3**[14] diastereoselectivity was improved at the expense of enantioselectivity (80% *ee*, entry 2), while the related cyclohexyldiamine-derived squaramide catalyst **C4**[15] afforded product **5Aa** with high *ee*, but yet suboptimal diastereoselectivity (dr 4:1, 92% *ee*, entry 3). After additional screening that showed thiourea catalysts inferior in reactivity and selectivity (e.g. **C5**, entry 4), we finally found that the reaction in the presence of newly developed catalyst **C6**[16] afforded the desired product **5Aa** in 82% yield, a remarkable 19:1 *dr* and 94% *ee* (entry 5). While the superior behavior of catalyst **C6** correlates well with previous observations,[16] it seems that its origin cannot be explained by steric congestion merely as the bulky neopentyl-derived catalyst **C7** was comparatively inferior (entry 6).



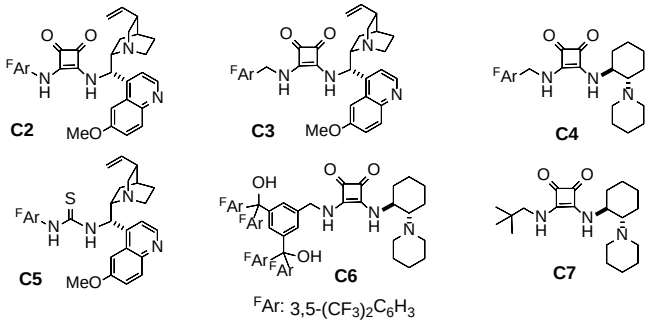
Scheme 2. Catalytic addition of alkenyl ynones **3** to nitroolefins and catalysts employed in this study.

As data in Table 2 show, the catalytic addition of **3A** to aromatic nitroolefins **4b** and **4e** worked equally well and adducts **5Ab** and **5Ae** were obtained in good yield and high selectivity. The reaction was also very selective with the β-alkyl substituted nitroolefin **4i**, although, as expected, progressed more slowly (44% conversion after 3 h). Ynone substrates with other aromatic substituents at the alkynyl moiety (adducts **5Ba**, **5Ca**) or even alkyl substituents

Table 1. Catalyst screening for the reaction of **3A** with **4a** to give **5Aa**[a] and catalysts described in these manuscript.

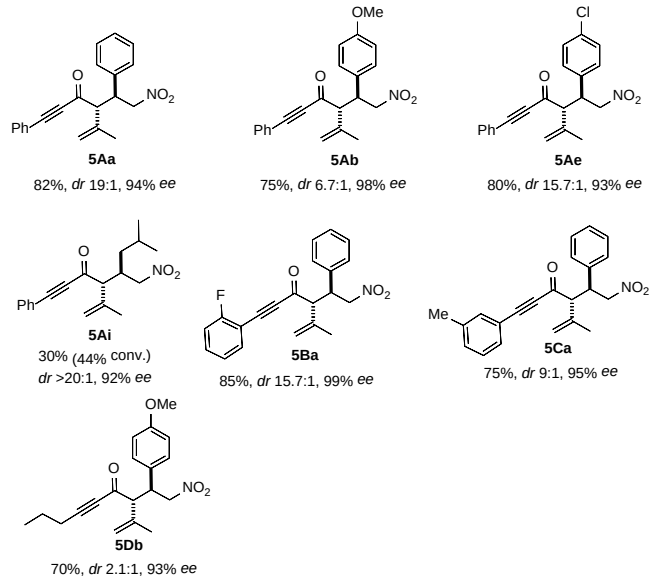
Entry	Cat	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**C2**		80	1.5:1	98
2	**C3**		80	10:1	80
3	**C4**		77	4:1	92
4	**C5**		70[e]	1:1	40
5	**C6**		**82**	**19:1**	**94**
6	**C7**		90[f]	5.7:1	59

5Aa



[a] Reactions run at 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3A**/**4a**/cat 2:1:0.1. [b] Combined yield of diastereomers after chromatography. [c] Determined by chiral HPLC after filtration through a short path of SiO_2. [d] *Ee* of major diastereomer determined by chiral HPLC. [e] Reaction conversion. [f] Conversion after 3 h reaction; 73% isolated yield.

Table 2. C6-catalyzed conjugate addition of alkenyl ynones **3** to nitroolefins **4**.[a]

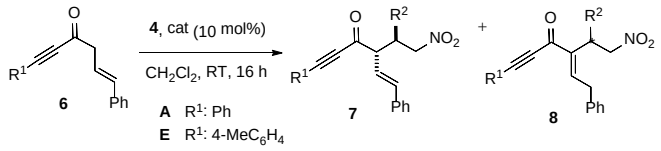


[a] Reactions run at 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **3**/**4**/catalyst 2:1:0.1. Variable amounts of isomerized starting material were observed in most entries; yield of major diastereomer after chromatography, except for **5Db** (combined yield). *Dr* and *ee* determined by chiral HPLC analysis.

(**5Db**) were well tolerated too. These results constitute the first evidence of Brønsted base catalyzed Michael additions of α,β-ynones that generate two adjacent tertiary stereocenters in highly enantio- and diastereoselective manner. One feature of these reactions is that whilst isomerization of the double bond on the newly formed adducts was not observed, the starting allyl ynones **3** isomerized to the respective vinyl ynones to some extent. However, the impact of this process on the reaction yield was negligible upon the use of two equivalents of the starting ynone. Some control experiments to assess the stability of products towards epimerization or double bond isomerization under the reaction conditions employed were carried out. For instance, when a solution of each adduct **5** was stirred at room temperature overnight in the presence of 10 mol% **C4** or **C6**, no change in the configurational integrity of adducts, nor appreciable isomerization, were observed.

We next studied the reaction outcome involving allyl ynones with a 1,2-disubstitution pattern on the olefin, which turned out to be strongly catalyst-dependent. Thus, as Table 3 shows, the reaction of **6A** with nitrostyrene **4a** in the presence of catalyst **C4** at room temperature overnight led to a mixture of adduct **7Aa** and its isomer **8Aa** in a 66:34 ratio (entry 1). In contrast, the same reaction promoted by catalyst **C6** cleanly led to **7Aa** as the only isolated product, which was obtained as a mixture of diastereomers each in very high enantioselectivity (entry 2). A similar trend was observed in the reactions of ynone **6A** with nitroolefins **4c** and **4f**, and of ynone **6E** with **4a**. Thus, exclusive formation of the α-addition products **7Ac**, **7Af** and **7Ea** was observed using catalyst **C6** (entries 4, 6 and 7), whereas with catalyst **C4** mixtures of products **7** and **8** were obtained in ratios of 83:17 and 81:19, respectively (entries 3 and 5). As before, control experiments with adducts **7** (unaltered material recovered after stirring a solution of the adduct in the presence of 10 mol% **C6** at room temperature overnight) demonstrated their stability towards double bond isomerization or epimerization. Two general conclusions can be brought from these and the previous[11] results involving vinylogous alkynyl ketone enolates: (i) Brønsted base catalyzed additions of allyl alkynyl ketones proceed in all cases tested with high Cα selectively, and (ii) the tendency of the allylic ynone products towards double bond isomerization depends primarily on the alkene substitution pattern, but also the catalyst employed. Isomerization can be totally cancelled by choosing the right Brønsted base catalyst, e.g. **C6**, providing adducts with two contiguous stereocenters in very high enantioselectivity and diastereomeric ratios from moderate to excellent.

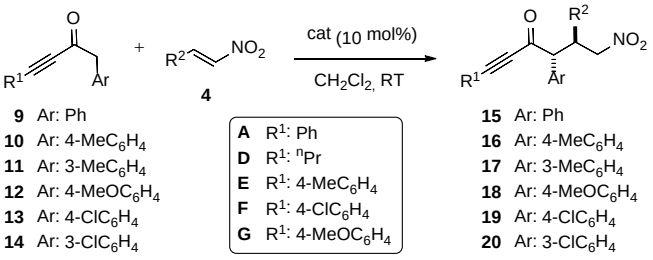
Table 3. Reaction of α-alkenyl ketones **6**: no isomerization with catalyst **C6**.[a]



Entry	R^1	R^2	Cat	Ratio[b] **7/8**	Yield of **7** [%][c]	d.r.[b]	*ee* [%][d]
1	Ph	Ph	**C4**	66:34	38	1.3:1	88 / 90
2	Ph	Ph	**C6**	>95:5	56	1:1	94 / >98
3	Ph	4-MeC_6H_4	**C4**	83:17	47	1.2:1	91 / 89
4	Ph	4-MeC_6H_4	**C6**	>95:5	62	1.4:1	95 / 85
5	Ph	2-ClC_6H_4	**C4**	81:19	46	1.2:1	96 / 93
6	Ph	2-ClC_6H_4	**C6**	>95:5	47	1:1	95 / 83
7	4-MeC_6H_4	Ph	**C6**	>95:5	58	1.4:1	94 / 79

[a] Reactions run at 0.2 mmol scale in 0.6 mL CH_2Cl_2; mol ratio of **6**/**4**/cat 2:1:0.1. [b] Determined by ^1H NMR. [c] Yield of pure **7** after chromatography. [d] *Ee* of each diastereomer determined by chiral HPLC.

Benzylic alkynyl ketones as nucleophiles. Although the above results were encouraging, the question of whether this method is suitable for a broader range of ynone compounds remained unanswered so far. Particularly, simple alkyl ynones, such as methyl ynones, had been previously shown unable to react with nitrostyrene in the presence of typical Brønsted base catalysts.[10] However, recent work by our own group revealed some particularly active benzylic ketones to be amenable substrates for Brønsted base-assisted activation.[15] Accordingly, benzylic ynones were envisioned as candidates for the evaluation of the method generality. A range of benzylic ynones **9**–**14** were easily accessible for the reaction screening which was initiated with ynone **9A** and β-aryl substituted nitroolefin **4b** in the presence of



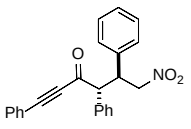
Scheme 3. Catalytic reaction of benzylic ynones **9**–**14** and nitroolefins **4**.

Table 4. Catalyst screening for the reaction of ynone **9A** and nitroolefin **4b** to yield adduct **15Ab**.[a]

Entry	Cat	t [h]	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	**C2**	2.5	95	1:1	ND
2	**C3**	2.5	96	2.8:1	82 (92)
3	**C4**	4.5	99	3.3:1	91 (97)
4	**C6**	6	97	5.7:1	96 (99)
5	**C7**	6	90	1.5:1	--

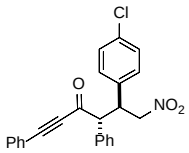
[a] Reactions run at 0.1 mmol scale in 0.3 mL CH_2Cl_2; mol ratio of **9A**/**4b**/cat 1:1.2:0.1. [b] Combined yield of diastereomers after chromatography. [c] Determined by chiral HPLC before chromatography. In parentheses the *ee* of minor isomer.

Table 5. Scope of the catalytic, enantioselective addition of alkynyl ketones **9**–**14** to nitroolefins **4**.[a]



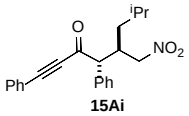
15Aa

C4 3 h 80%, *dr* 5.7:1, 93% *ee* (98% *ee*)
C6 4 h 86%, *dr* 4.9:1, 96% *ee* (99% *ee*)



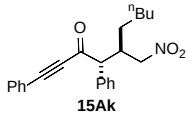
15Ae

C4 3 h 99%, *dr* 3.3:1, 94% *ee* (98% *ee*)
C6 6 h 93%, *dr* 5.2:1, 99% *ee* (99% *ee*)



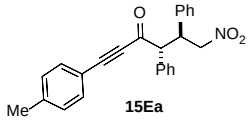
15Ai

C6 144 h, 71%[b], *dr* 2.6:1, 94% *ee* (98% *ee*)



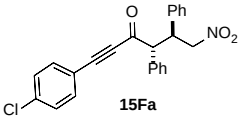
15Ak

C6 144 h, 68%[c], *dr* 2.8:1, 94% *ee* (88% *ee*)



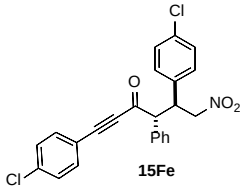
15Ea

C6 16 h, 87%, *dr* 4:1, 96% *ee* (*ee* nd)



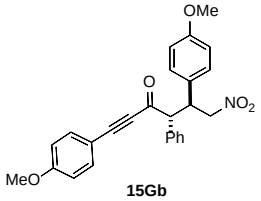
15Fa

C4 16 h, 77%, *dr* 2.7:1, 90% *ee* (98% *ee*)
C6 16 h, 87%, *dr* 3:1, 96% *ee* (99% *ee*)



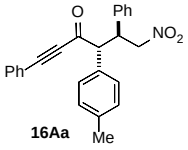
15Fe

C4 16 h, 77%, *dr* 3.3:1, 90% *ee* (98% *ee*)
C6 16 h, 90%, *dr* 4.6:1, 92% *ee* (99% *ee*)



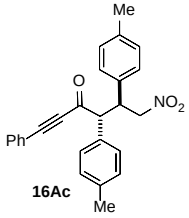
15Gb

C6 16 h, 86%, *dr* 6.7:1, 94% *ee* (99% *ee*)



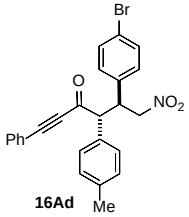
16Aa

C4 3 h, 85%, *dr* 3.2:1, 90% *ee* (99% *ee*)
C6 16 h, 90%, *dr* 4.9:1, 84% *ee* (99% *ee*)



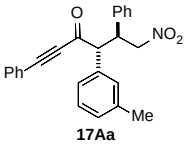
16Ac

C6 16 h , 90%, *dr* 4.9:1, 96% *ee* (98% *ee*)



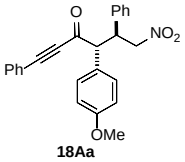
16Ad

C4 4 h, 89%, *dr* 2.6:1, 94% *ee* (98% *ee*)
C6 16 h, 93%, *dr* 6.7:1, 96% *ee* (99% *ee*)



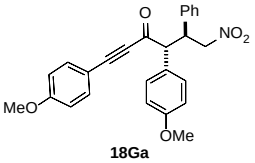
17Aa

C6 16 h, 96%, *dr* 6.1:1, 94% *ee* (99% *ee*)



18Aa

C6 16 h, 96%, *dr* 4:1, 96% *ee* (99% *ee*)



18Ga

C6 16 h, 96%, *dr* 8.1:1, 98% *ee* (99% *ee*)

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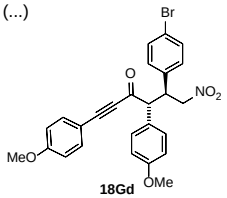
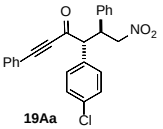


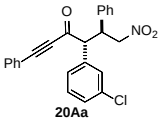
18Gd

C6 16 h, 82%, *dr* 6.7:1, 96% *ee* (99% *ee*)



19Aa

C4 5 h, 41%, *dr* 8.1:1, 98% *ee* (92% *ee*)
C6 16 h, 30%, *dr* 10.1:1, 98% *ee* (99% *ee*)



20Aa

C6 16 h, 88%, *dr* 6.1:1, 95% *ee* (99% *ee*)

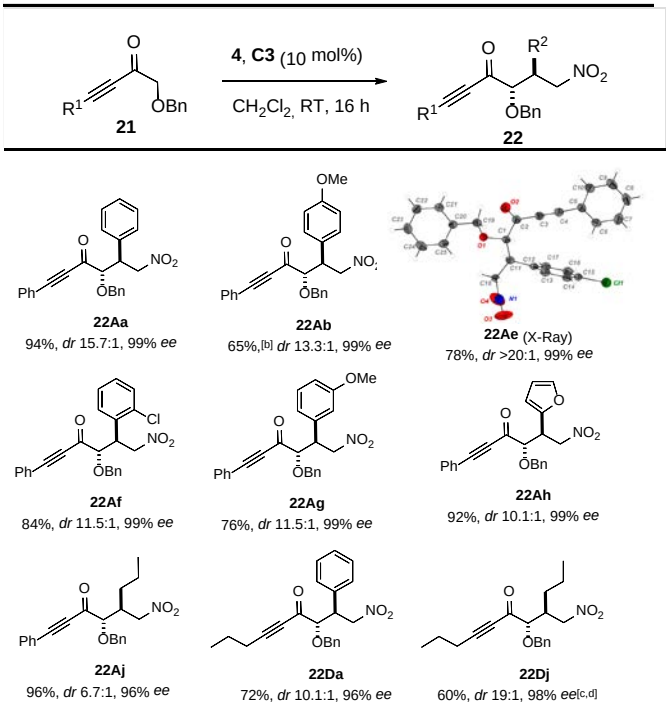
[a] Reactions run at 0.1 mmol scale in 0.3 mL CH_2Cl_2; mol ratio of **9**–**14**/**4**/cat 1:1.2:0.1. Combined yield of diastereomers after chromatography; *dr* and *ee* determined by chiral HPLC. In parentheses the *ee* of minor isomer. [b] Conversion of 84%. [c] Conversion of 74%.

several bifunctional squaramide catalysts.[13] As data in Scheme 3 and Table 4 show, the reaction in the presence of **C2** took place in a few hours to give product **15Ab** in good yield, albeit no diastereocontrol at all (entry 1). Diastereoselectivity was improved using catalyst **C3** (entry 2) and even more with **C4** (entry 3) that afforded product **15Ab** in 3.3:1 dr and 91% and 97% *ee*, respectively, for each isomer. Further screening showed catalyst **C6** the most selective once more (5.7:1 *dr*, 96% and 99% *ee*, entry 4), whilst its bis-*O*-trimethylsilyl analog (see the supporting information) led to slightly lower diastereoselectivity (3.2:1 *dr*, 98% and 99% *ee*). For comparative purposes, the reaction with catalyst **C7**, bearing a bulky neopentyl group at the squaramide terminus, was carried out, but again led to an almost equimolar mixture of diastereomers. These results support the initial assumption that steric effects alone may not suffice to explain the salient performance of **C6**. This trend in catalyst behavior was confirmed along the exploration of the reaction scope with regard to the nitroolefin. As shown in Table 5, when the reaction of **9A** with **4a** and **4e** was promoted by catalysts **C4** and **C6** similar results were produced albeit the latter provided somewhat better diastereoselectivity. β-Alkyl substituted nitroolefins as well as a variety of electron-poor, and rich, β-aryl substituted nitroolefins participate well in the reaction of alkynylketones **9**-**14** to afford adducts **15**-**20** in very high yield, good diastereoselectivity and nearly perfect enantioselectivity for most cases, independently of the substitution pattern of each reaction component. The absolute configuration of adduct **15Ab** was established by single crystal X-ray structure analysis[17] and for the remaining adducts was assumed by analogy on the bases of a uniform reaction mechanism.

Benzyloxymethyl alkynyl ketones as nucleophiles. In view of the successful reactivity of both benzyl and allyl ynones, the behavior of ynones with an alkoxymethyl sidechain was explored next. The heteroatom-substituted sidechain would not only render synthetically appealing adducts, but also increased acidity to substrates for Brønsted base catalyst activation. Concordant with our expectations, it was found that ynones **21**, bearing a

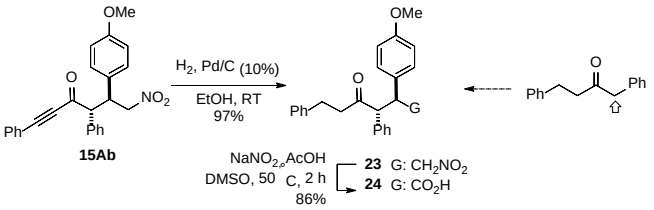
benzyloxymethyl side-arm, are indeed competent for the catalyzed reaction with nitroolefins. Among the catalysts examined for these reactions,[13] **C3** resulted superior. For example, as data in Table 6 show, the reactions of **21A** with nitrostyrenes **4a-g** in the presence of 10 mol% **C3** afforded adducts **22Aa**-**g** in excellent diastereomeric ratio (typically greater than 10:1) and *ee*'s up to 99% for the major diastereomer. The reaction with the β-heteroaromatic nitroolefin **4h**, or the most challenging alkyl nitroolefin **4j**, also provided the corresponding adducts **22Ah**, **22Aj** in very good yields, diastereomeric ratios of 10:1 and 6.7:1, and enantioselectivities of 99% and 96%, respectively. Similarly, the alkyl substituted ynone **21D** reacted smoothly with either aromatic or aliphatic nitroolefins giving access to adducts **22Da**, **22Dj** in nearly perfect stereoselectivity. Absolute configuration of adduct **22Ae** was established by single crystal X-Ray structure analysis[17] and for the remaining adducts **22** was assumed by analogy on the bases of a uniform reaction mechanism.

Table 6. Catalytic, enantioselective reaction of benzyloxy ynones **21** with nitroolefins **4**.[a]



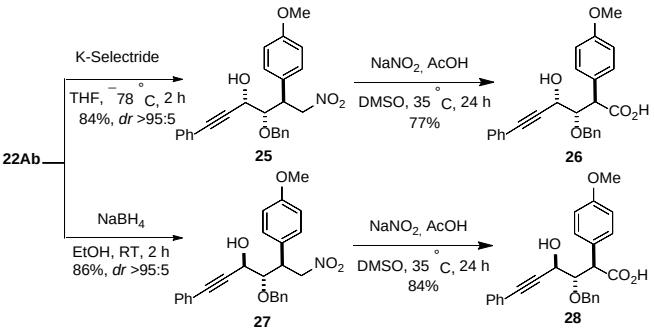
[a] Reactions run at 0.2 mmol scale in 0.2 mL CH_2Cl_2; mol ratio of **21**/**4**/catalyst 1:2:0.1. Yields of isolated product after chromatography; *ee* determined by chiral HPLC before chromatography. [b] 80% conversion after 72 h. [c] Reaction run at 0.2 mmol scale in 0.2 mL 1,2-DCE using 3 equiv. of nitroolefin. [d] 65% conversion after 48 h.

Elaboration of adducts. An interesting aspect of the above catalytic reactions is that adducts can be transformed into polyfunctionalized structures with two or more contiguous tertiary stereocenters using simple chemical protocols. For instance, reduction of the alkynyl moiety in adducts provides dissymmetric alkyl alkyl ketone products with two tertiary stereocenters at α and β positions. For instance, catalytic hydrogenation of **15Ab** afforded **23** in 97% yield (Scheme 4), the α-branched ketone product formally derived from the yet unrealized site- and stereoselective α-alkyltion of the corresponding phenethyl ketone.



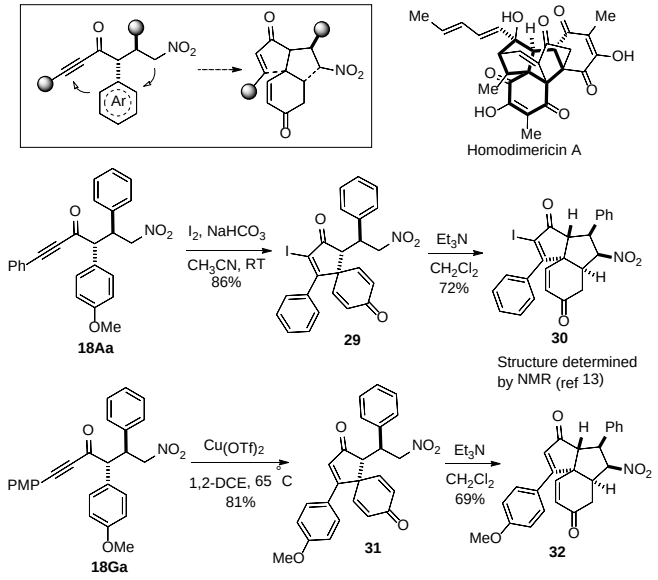
Scheme 4. Reduction of adducts to α-branched alkyl alkyl ketones.

Alternatively, substrate-controlled stereoselective reduction of the ketone carbonyl to carbinol was feasible according to two stereodivergent pathways (Scheme 5). On the one hand, reduction of **22Ab** with K-Selectride proceeded via a Felkin-Anh model[18] to afford *syn* alcohol **25** exclusively, while chelation controlled reduction with $NaBH_4$ afforded the complementary *anti* alcohol[19] **27**, in both cases with good isolated yields. The nitro group in these molecules is amenable for efficient transformation into a carboxylic acid function upon oxidation according to Mioskowski[20] conditions, as illustrated by the conversion of **23** to acid **24** (86%) (Scheme 4), **25** to **26** (77%) and **27** to **28** (84%), respectively, Scheme 5.



Scheme 5. Diastereodivergent reduction of the ketone carbonyl to *syn* and *anti*-diol units.

Further synthetic interest of the present catalytic addition reactions is derivable from intramolecular carbofunctionalizations of the alkynyl moiety in adducts. As shown in Scheme 6, Larock's ipso-halocyclisation[21] of adduct **18Aa** furnished spirocycle **29** in 86% yield, while heating adduct **18Ga** at 65 °C in the presence of Cu(II), according to the method of Taylor and Unsworth,[22] led to the spirocycle **31**. These spirocyclic quinones are easily converted into compounds **30** and **32**, respectively, which display a tricyclic carbon core similar to that present in homodimericin A,[23] a structurally intricate compound whose enantioselective chemical synthesis is still pending.[24]



Scheme 6. Elaboration of adducts into carbocycles of intricate structure.

Conclusions

In conclusion, conjugate additions of enolizable α,β-ynones to nitroolefins is feasible in a highly selective fashion in the presence of tertiary amine/squaramide bifunctional catalysts, affording an atom economic route to densely functionalized building-blocks. For the new C–C bond forming reaction not only allyl ynones, but also benzylic ynones and alkoxymethyl ynones are suitable ketone donors, thus complementing the few existing direct approaches for the α-functionalization of alkynyl ketones. Elaboration of the α-branched ynone adducts through simple protocols allows an access to stereochemically complex structures, both acyclic and intricate tricyclic carbon skeletons, in optically pure form.

Experimental Section

General Procedure for the Michael reaction: To a solution of the corresponding ynone (0.1 mmol, 1 eq.) and nitroalkene (0.12 mmol, 1.2 eq.) in dichloromethane (0.3 mL) at room temperature the catalyst (0.01 mmol, 10 mol %) was added and the resulting mixture was stirred at the same temperature for the time indicated in the tables. Then the mixture was directly submitted to a flash column chromatography (eluent hexane/ethyl acetate).

Compound 15Ab: The title compound was prepared from 1,4-diphenylbut-3-yn-2-one (**9A**) (22.0 mg, 0.1 mmol) according to the general procedure with cat **C6**, affording a 5.7:1 mixture of diastereomers. Yield: 38.6 mg, 97%. Crystallized from Et_2O. White solid. $[\alpha]_D^{25}$= –62.9° (*c*= 0.53, 96% *ee*, CH_2Cl_2). m.p. 156–158 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.59–7.29 (m, 12H), 6.89 (d, *J*= 8.7 Hz, 2H), 4.56–4.28 (m, 4H), 3.79 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 160.0, 134.8, 133.7, 131.6, 130.3, 129.9, 129.6, 129.5, 129.3, 120.2, 115.1, 110.7, 94.0, 88.1, 79.6, 64.5, 55.9, 45.5. UPLC-DAD-QTOF: $C_{25}H_{22}NO_4$ $[M+H]^+$ calcd.: 400.1549, found: 400.1550.

Compound 18Aa: Prepared from 1-(4-methoxyphenyl)-4-phenylbut-3-yn-2-one (**12A**) (25.0 mg, 0.1 mmol) according to the general procedure with cat **C6**, affording a 4.1:1 mixture of diastereomers. Yield: 38.34 mg, 96 %. Crystallized from Et_2O. White solid. $[\alpha]_D^{25}$= –55.5° (*c* = 0.3, 96% *ee*, CH_2Cl_2). m.p. 134–136 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.52–7.26 (m, 14H), 6.99 (d, *J*= 8.7 Hz, 2H), 4.53–4.32 (m, 4H), 3.85 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 182.7, 158.8, 136.1, 131.8, 129.7, 128.9, 127.8, 127.4, 127.0, 126.9, 124.6, 118.4, 113.9, 92.0, 86.3, 78.0, 61.5, 54.1, 44.3. UPLC-DAD-QTOF: $C_{25}H_{22}NO_4$ $[M+H]^+$ calcd.: 400.1549, found:400.1551.

Compound 18Ga: Prepared from 1,4-bis(4-methoxyphenyl)but-3-yn-2-one (**12G**) (28.0 mg, 0.1 mmol) according to the general procedure with cat **C6**, affording a 8.1:1 mixture of diastereomers. Yield: 41.2 mg, 96 %. Crystallized from Et_2O. White solid. $[\alpha]_D^{25}$= –1.4° (*c* = 0.2, 98% *ee*, CH_2Cl_2). m.p. 142–144 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 (d, *J*= 9.0 Hz, 2H), 7.40 (d, *J*= 8.7 Hz, 2H), 7.38–7.29 (m, 5H), 6.98 (d, *J*= 8.8 Hz, 2H), 6.88 (d, *J*= 8.9 Hz, 2H), 4.51–4.30 (m, 4H), 3.85 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.6, 160.6, 138.1, 135.8, 131.7, 130.7, 129.6, 128.8, 128.7, 128.2, 126.7, 115.7, 115.0, 110.7, 95.0, 88.3, 79.6, 63.3, 56.0, 46.3 UPLC-DAD-QTOF: $C_{26}H_{24}NO_5$ $[M+H]^+$ calcd.: 430.1654, found: 430.1658. UPLC-DAD-QTOF: $C_{26}H_{23}NO_5Na$ $[M+Na]^+$ calcd.: 452.1474, found:452.1470.

Compound 22Ab: Prepared starting from ynone **21A** (50 mg, 0.2 mmol) according to the general procedure with cat **C3**. Orange oil, yield: 56 mg (65 %). $[\alpha]_D^{25}$ = +26.1° (c= 1, >99% *ee*, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.28 (m, 11H), 7.25–7.18 (m, 2H), 6.90–6.82 (m, 2H), 4.95–4.68 (m, 4H), 4.46 (d, *J*= 11.3 Hz, 1H), 4.15 (ddd, *J*= 9.3, 7.0, 4.9 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 160.6, 137.5, 134.5, 132.4, 131.4, 130.5, 129.8, 129.7, 129.4, 129.3, 128.2, 120.4, 115.5, 87.4, 87.2, 77.7, 74.2, 56.3, 46.6. UPLC-DAD-QTOF: $C_{26}H_{24}NO_5$ $[M+H]^+$ calcd.: 430.1654, found: 430.1654.

***Syn* selective reduction of 22Ab:** To a solution of **22Ab** (0.2 mmol, 86 mg) in dry THF (0.5 mL) at −78 °C a solution of K-selectride in THF (1M, 3 equiv., 0.6 mmol, 0.6 mL) was added and the mixture was stirred at that temperature for 2 hours. Then water (0.2 mL) and EtOH (0.4 mL) were successively added, and after 5 min of stirring H_2O_2 (30%, 0.4 mL) was added. The reaction mixture was allowed to rise to room temperature and the mixture was stirred for an additional 10 min. Then, it was diluted with EtOAc (5 mL) and water (5 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), the organic layers were combined, and dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to afford compound **25** as a yellow oil (dr: >95:5). Yield: 70 mg (84%). $[\alpha]_D^{25}$ = +3.4° (*c*= 0.1, CH_2Cl_2, from adduct of >99 % *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46–7.26 (m, 10H), 7.20–7.15 (m, 2H), 6.92–6.87 (m, 2H), 5.13 (d, *J*= 10.9 Hz, 1H), 4.91–4.84 (m, 1H), 4.84–4.79 (m, 1H), 4.62–4.49 (m, 1H), 4.39 (d, *J*= 1.4 Hz, 1H), 4.00–3.93 (m, 2H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 150.8, 138.1, 132.7, 131.2, 130.4, 129.9, 129.8, 129.6, 129.6, 129.5, 115.8, 89.6, 84.1, 78.8, 76.5, 63.1, 56.4, 46.4, 30.8. DAD-QTOF: $C_{26}H_{26}NO_5$ $[M+H]^+$ calcd.: 432.1811, found: 432.1814.

***Anti* selective reduction of 22Ab:** $NaBH_4$ (16 mg, 0.4 mmol, 2 equiv.) was added to a stirred mixture of compound **22Ab** (0.2 mmol, 86 mg) in EtOH (1 mL) at room temperature. After 2 h the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and brine (5 mL), and dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography (eluent hexane/ethyl acetate 80:20) to afford compound **27** as a colourless oil (dr: >95:5). Yield: 74 mg (86 %). $[\alpha]_D^{25}$ = +18.3° (*c*= 0.3, CH_2Cl_2, from adduct of >99% *ee*). ^{1}H NMR (400 MHz,

$CDCl_3$), δ: 7.50–7.25 (m, 10H), 7.24–7.20 (m, 2H), 6.89–6.84 (m, 2H), 5.02 (dd, *J*= 12.9, 5.0 Hz, 1H), 4.88 (d, *J*= 11.4 Hz, 1H), 4.73–4.62 (m, 2H), 4.59 (d, *J*= 3.5 Hz, 1H), 4.03 (ddd, *J*= 9.8, 7.5, 5.1 Hz, 1H), 3.93 (dd, *J*= 7.5, 3.5 Hz, 1H), 3.84–3.82 (m, 1H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$), δ: 159.2, 137.4, 131.8, 129.2, 129.0, 128.8, 128.7, 128.3, 128.2, 128.1, 122.0, 114.4, 83.3, 74.7, 64.7, 55.2, 45.2, 29.7. DAD-QTOF: $C_{26}H_{26}NO_5$ $[M+H]^+$ calcd.: 432.1811, found: 432.1810.

Procedure for the Nef oxidation of adducts 23, 25 and 27: (Mioskowski conditions) A solution of the corresponding diol (1 equiv.), sodium nitrite (3 equiv.) and acetic acid (10 equiv.) in DMSO (0.5 mL/0.2 mmol) was stirred at 35 or 50 °C for 24 h. After this period, the reaction mixture was quenched with HCl 1N (5 mL) and the mixture was extracted with Et_2O (4 × 5 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting crude material was purified by flash column chromatography.

Compound 24: Prepared from compound **23** (65 mg, 0.16 mmol) according to the general procedure. White solid, yield 53.8 mg (86%). $[\alpha]_D^{25}$= –129.6° (*c*= 0.1, CH_2Cl_2, from adduct of 96% *ee*). m.p. 144–146 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.40–6.80 (m, 14H), 4.53–4.33 (m, 2H), 3.82 (s, 3H), 2.77–2.32 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 207.6, 177.6, 160.3, 141.6, 136.5, 133.4, 130.7, 130.0, 129.8, 129.4, 129.1, 129.0, 127,0, 115.3, 62.3, 56.3, 54.1, 45.4, 30.1. UPLC-DAD-QTOF: $C_{25}H_{24}O_4Na$ $[M+Na]^+$ calcd.: 411.1572, found:411.1570.

Compound 26: Prepared from compound **25** (86 mg, 0.2 mmol) according to the general procedure. Colourless oil, yield 64 mg (77%). $[\alpha]_D^{25}$ = +13.5° (*c*= 0.3, CH_2Cl_2, from adduct of 99% *ee*). IR (ν/ cm^{-1}): 3356 (O–H), 1716 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.00–7.91 (m, 2H), 7.55–7.43 (m, 3H), 7.34–7.24 (m, 3H), 7.23–7.14 (m, 2H), 7.12–7.03 (m, 2H), 6.95–6.86 (m, 2H), 5.36 (d, *J*= 4.2 Hz, 1H), 4.77 (d, *J*= 6.6 Hz, 1H), 4.54 (dd, *J*= 6.6, 4.3 Hz, 1H), 4.48 (q, *J*= 11.7 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$), δ: 171.9, 164.4, 159.1, 137.6, 130.6, 130.5, 129.2, 128.6, 128.2, 128.1, 127.7, 127.4, 127.1, 117.9, 114.2, 94.1, 72.8, 72.7, 55.6, 53.7, 45.3, 29.9. DAD-QTOF: $C_{26}H_{25}NO_5$ $[M+H]^+$ calcd.: 417.1702, found: 417.1702.

Compound 28: Prepared from compound **27** (86 mg, 0.2 mmol) according to the general procedure. Yield: 70 mg (84%). $[\alpha]_D^{25}$ = +27.5° (*c*= 0.4, CH_2Cl_2, from adduct of 99% *ee*). IR (ν/ cm^{-1}): 3500 (O–H), 1731 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.06–7.94 (m, 2H), 7.58–7.40 (m, 2H), 7.37 (d, *J*= 8.6 Hz, 5H), 7.32–7.25 (m, 2H), 7.12–7.06 (m, 1H), 6.93 (d, *J*= 8.7 Hz, 2H), 5.27 (dd, *J*= 7.5, 5.1 Hz, 1H), 4.66 (dd, *J*= 5.9, 5.1 Hz, 1H), 4.52 (d, *J*= 5.9 Hz, 1H), 4.35–4.21 (m, 2H), 3.85 (s, 3H), 3.13 (d, *J*= 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 172.3, 165.1, 159.8, 137.4, 131.4, 130.9, 129.6, 129.2, 128.9, 128.9, 128.0, 128.0, 127.5, 120.2, 114.6, 88.9, 77.9, 74.6, 68.3, 56.0, 47.0, 30.4. DAD-QTOF: $C_{26}H_{25}NO_5$ $[M+H]^+$ calcd.: 417.1702, found: 417.1698.

Preparation of spirocycle 29: To a solution of adduct **18Aa** (1 eq., 0.1 mmol, 40 mg.) in CH_3CN (0.3 mL) at room temperature was added I_2 (3 eq., 0.3 mmol, 76 mg) and $NaHCO_3$ (2 eq., 0.2 mmol, 17 mg). The reaction mixture was stirred at room temperature overnight, then it was diluted with Et_2O and washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure, and the resulting product was crashed with hexane to afford a brown foam. Yield: 44 mg (86%). $[\alpha]_D^{25}$= –11.8º (*c*= 1.0, CH_2Cl_2, from adduct of 96% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46–7.21 (m, 9H), 7.13 (d, *J*= 7.9 Hz, 2H), 6.79 (dd, *J*= 10.0, 2.6 Hz, 1H), 6.39 (dd, *J*= 10.0, 1.4 Hz, 1H), 6.27–6.16 (m, 2H), 5.22 (dd, *J*= 13.4, 7.5 Hz, 1H), 4.89 (dd, *J*= 13.4, 7.6 Hz, 1H), 3.90–3.64 (m, 2H), 3.54 (d, *J*= 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 200.1, 184.9, 175.8, 148.5, 147.7, 136.9, 134.4, 132.6, 132.5, 131.2, 130.6, 129.8, 129.3, 129.2, 127.5, 106.1, 78.8, 59.4, 57.31, 43.5, 30.5. UPLC-DAD-QTOF: $C_{24}H_{19}INO_4$ $[M+H]^+$ calcd.: 512.0359, found: 512.0362. UPLC-DAD-QTOF: $C_{24}H_{18}NO_4INa$ $[M+Na]^+$ calcd.: 534.0178, found:534.0184.

Preparation of spirocycle 31: To a solution of adduct **18Ga** (1 eq., 0.13 mmol, 55 mg) in 1,2-DCE (1mL) was added $Cu(OTf)_2$ (1 eq., 0.13 mmol, 47 mg). The reaction mixture was stirred at 65 ºC for 3 h. Then the mixture was filtered, rinsed with CH_2Cl_2 and concentrated in vacuo to afford a brown foam. $[\alpha]_D^{25}$= –9.5º (*c*= 1.5, CH_2Cl_2, from adduct of 98% *ee*). Yield: 44 mg (81%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.41 (d, *J*= 8.7 Hz, 3H), 6.93 (d, *J*= 8.1 Hz, 1H), 6.82 (d, *J*= 8.8 Hz, 2H), 6.65 (s, 1H), 6.56 (d, *J*= 10.1 Hz, 1H), 6.34–6.12 (m, 2H), 5.24 (dd, *J*= 13.2, 7.5 Hz, 1H), 5.02–4.84 (m, 1H), 3.81 (s, 3H), 3.65 (td, *J*= 7.2, 3.5 Hz, 1H), 3.32 (d, *J*= 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 204.2, 185.4, 173.1, 163.3, 151.4, 151.1, 137.4, 131.0, 130.1, 129.6, 128.9, 127.7, 125.6, 115.1, 94.1, 79.4, 73.8, 56.3, 56.1, 43.1, 30.3. UPLC-DAD-QTOF: $C_{25}H_{22}NO_5$ $[M+H]^+$ calcd.: 416.1498, found: 416.1501. UPLC-DAD-QTOF: $C_{25}H_{21}NO_5Na$ $[M+Na]^+$ calcd.: 438.1317, found:438.1314.

Preparation of tricycles 30 and 32: To a solution of the corresponding spirocyclic compound **29** or **31** (1 eq., 0.1 mmol) in dichloromethane (0.6 mL) was added Et_3N (20 eq., 2 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was directly submitted to a non-acidic silica gel column chromatography (eluent hexane/AcOEt 95:5→ 90:10).

Compound 30: Prepared from compound **29** (51.1 mg, 0.1 mmol) according to the general procedure. Brown foam, yield: 36.8 mg (72%). $[\alpha]_D^{25}$= –35.1º (*c*= 0.3, CH_2Cl_2, from adduct of 96% *ee*). Decomp. 135 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.63–7.23 (m, 10H), 6.81 (dd, *J*= 10.2, 1.6 Hz, 1H), 6.36 (dd, *J*= 10.2, 0.7 Hz, 1H), 5.00 (t, *J*= 11.2 Hz, 1H), 3.96–3.84 (m, 1H), 3.24 (d, *J*= 9.1 Hz, 1H), 3.21–3.11 (m, 1H), 2.37 (d, *J*= 17.7 Hz, 1H), 1.94 (dd, *J*= 17.8, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 199.9, 194.2, 176.7, 147.7, 136.8, 134.8, 131.3, 131.2, 130.1, 129.8, 129.2, 128.0, 127.6, 105.5, 94.7, 60.3, 50.7, 47.3, 35.7. UPLC-DAD-QTOF: $C_{24}H_{18}NO_4INa$ $[M+Na]^+$ calcd.: 534.0175, found:534.0184.

Compound 32: Prepared from compound **31** (41.5 mg, 0.1 mmol) according to the general procedure. Brown solid, yield: 28.7 mg (69%). $[\alpha]_D^{25}$= –9.0º (*c*= 0.4, CH_2Cl_2, from adduct of 98% *ee*). Decomp. 130 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.62 (d, *J*= 8.9 Hz, 2H), 7.46–7.24 (m, 5H), 7.05–6.90 (m, 3H), 6.45 (d, *J*= 10.2 Hz, 1H), 6.34 (s, 1H), 4.99 (t, *J*= 11.1 Hz, 1H), 3.89 (s, 3H), 3.84 (d, *J*= 10.9 Hz, 1H), 3.21–3.12 (m, 1H), 3.10 (d, *J*= 9.5 Hz, 1H), 2.61–2.56 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 203.9, 195.0, 174.9, 163.0, 150.7, 137.0, 130.3, 129.1, 128.2, 128.1, 126.7, 115.4, 96.0, 63.9, 56.2, 51.2, 46.7, 36.8. UPLC-DAD-QTOF: $C_{25}H_{22}NO_5$ $[M+H]^+$ calcd.: 416.1498, found:416.1500.

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Keywords: asymmetric catalysis • Brønsted bases • Michael reaction • organocatalysis • alkynyl ketones

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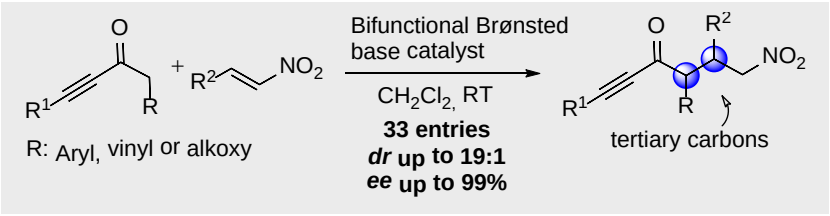

Donor ynones: under very mild conditions linear ynones with no additional EWG at Cα get activated by tertiary amine/squaramide chiral catalysts and react with nitroolefins in a highly diastereo- and enantioselective fashion. This way, an easy entry to branched alkyl alkynyl ketones with two contiguous stereocenters and derivatives thereof is provided.

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Enantioselective Addition of Alkynyl Ketones to Nitroolefins Assisted by Brønsted Base/H-Bonding Catalysis.