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Practical Asymmetric Conjugate Alkynylation of Meldrum's Acid-Derived Acceptors: Access to Chiral β-Alkynyl Acids

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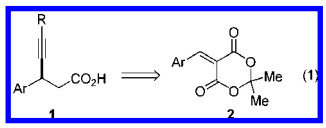
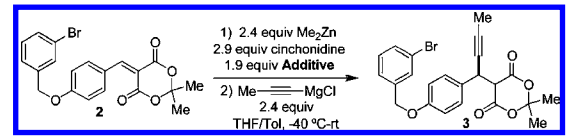
Chiral β-alkynyl acids are an important class of pharmaceutical compounds with diverse biological activities that include PDE IV inhibitors, TNF inhibitors, GPR40 receptor agonists, and GRP receptor antagonists.[1] However, because of the lack of available asymmetric methods, their preparation typically requires racemic synthesis followed by separation of enantiomers (classical resolution or chiral chromatography). In this context, the asymmetric conjugate alkynylation of an ester-derived acceptor represents a particularly direct route to this target class. Meldrum's acid-derived acceptors **2** (eq 1) are attractive substrates for such processes because they can be readily prepared by Knoevenagel condensation of Meldrum's acid with aldehydes and the challenges associated with the control and influence of olefin geometry are absent. Furthermore, the conjugate-addition products can be easily converted to the corresponding β-alkynyl acids **1** in high yield.[2]



Carreira and co-workers[3] recently reported the first example of copper-catalyzed enantioselective conjugate additions to Meldrum's acid-derived acceptors, providing a new avenue to optically enriched β-alkynyl acids. However, the effective nucleophile was limited to phenylacetylene, and aliphatic alkynes afforded significantly lower yield (<30%) and enantioselectivity (<70%) even in the presence of 20 mol % copper−PINAP catalyst. In fact, despite considerable progress in the area of enantioselective conjugate alkynylation over the past decade, bulky or electronically activated alkyne nucleophiles such as silyl- or arylacetylenes remain the alkynes of choice.[4] To the best of our knowledge, synthetically useful yields and enantioselectivities have never been achieved in enantioselective conjugate alkynylation of ester-derived acceptors with aliphatic alkyne nucleophiles. Herein we report a practical, general, and highly enantioselective conjugate alkynylation of Meldrum's acid-derived acceptors employing cinchonidine, an inexpensive and recyclable chiral mediator (<$100/kg). This process has been readily extended to a variety of alkynylides, including those possessing aliphatic, aromatic, and silyl groups, to afford products in both high yield and enantioselectivity.

Following an extensive screen,[5] we identified that reaction of a Zn alkynylide species prepared by treatment of MeC≡CMgCl with a chiral zinc alkoxide reagent generated by the reaction of Me_2Zn with the chiral amino alcohol cinchonidine and achiral additive trifluoroethanol afforded **3** in 96% yield and 90% ee (Table 1, entry 1).[6−8] Interestingly, a large selectivity disparity was observed when different achiral additives were used (entries 1−6), which prompted an in-depth investigation. While the conjugate addition reaction proceeded slowly in the presence of the bulky additive neopentanol (entry 3), a variety of carboxylic acids, including pivalic acid (entries 4−6), performed as effectively as trifluoroethanol (entry 1).[9] Importantly, as shown in entries 10−12, it was demonstrated that in addition to the primary chiral ligand (cinchonidine), a second chiral component (e.g., Mosher acid) can further modulate the chiral environment around the zinc atom, resulting in dramatically enhanced enantioselectivity (from 90 to 98% ee; entries 1 and 11), although the configuration of the additive did not change the major product configuration (entries 7−12). This novel finding in regard to tuning of chiral zincate selectivity should be applicable to other Zn-mediated asymmetric transformations.

Table 1. Zn-Mediated Asymmetric Conjugate Alkynylation



entry	Additive	% ee[a] (% yield[b])	entry	Additive	% ee[a] (% yield[b])
1	CF_3CH_2OH	90 (96)	7	(*R*)-$CF_3CH(CH_3)OH$	66 (96)
2	MeOH	64 (95)	8	(*S*)-$CF_3CH(CH_3)OH$	88 (95)
3	$(CH_3)_3CCH_2OH$	n.d.[c] (64)	9	(*rac*)-$CF_3CH(CH_3)OH$	80 (95)
4	CF_3COOH	75 (86)	10	(*R*)-Mosher acid	94 (94)
5	CH_3COOH	87 (89)	11	(*S*)-Mosher acid	98 (95)
6	$(CH_3)_3CCOOH$	90 (93)	12	(*rac*)-Mosher acid	97 (95)

[a] Determined by chiral HPLC. [b] Assay yields determined by quantitative HPLC. [c] Not determined.

The enantioselectivity of the process was not strongly dependent on the reaction temperature, and full conversion was generally reached at room temperature (rt).[10] The optimal ratio of chiral to achiral alcohol was determined to be 1.5:1. A slight increase in enantioselectivity was observed when the ratio of chiral to achiral alcohol was increased, but the reaction rate and yield decreased.[11] Little change in the enantioselectivity was observed when the amount of chiral zincate was reduced from 2.4 to 1.2 equiv.

To demonstrate the practicality of this new method, a reaction of substrate **2** was carried out on 10 g scale (Scheme 1). A chiral zincate **4**[12] was generated by treatment of Et_2Zn with cinchonidine and trifluoroethanol followed by addition of the Grignard reagent. The acceptor **2** was then added, and the mixture was aged for 24 h at rt. Following workup, the product **3** was isolated in 85% yield and >99% ee after a single crystallization. Notably, cinchonidine could be recovered from the aqueous layer in 95% yield by simple pH adjustment and filtration. Finally, the adduct **3** was readily converted to the β-alkynyl acid **1** in 96% yield without racemization.

Having established an optimal protocol, we next investigated the generality and the scope of the reaction. As the data in entries 1−9 of Table 2 illustrate, a wide range of functional groups were well-tolerated, including carbonate, nitrile, ester, and ketone. Altering the electronic character of the para and meta positions of the phenyl ring did not

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Scheme 1

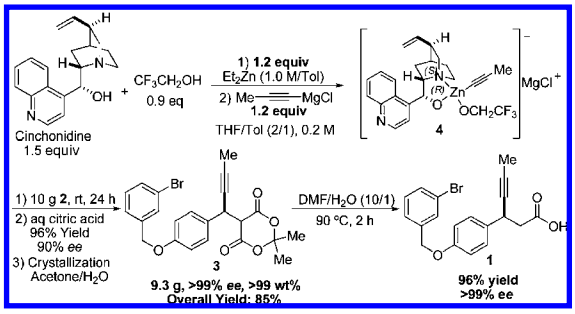
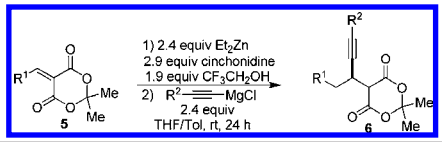


Table 2. Substrate Scope of Asymmetric Conjugate Alkynylation



entry	R^1	R^2	% yield[a]	% ee[b]
1	4-(MeO)Ph (**5a**)	Me	87 (76[c]) (**6a**)	93 (>99[c])
2	4-ClPh (**5b**)	Me	95 (**6b**)	94
3	4-BrPh (**5c**)	Me	96 (86[c]) (**6c**)	93 (>99[c])
4	4-(MeCO)Ph (**5d**)	Me	91 (**6d**)	93
5	4-(MeOOC)Ph (**5e**)	Me	90 (**6e**)	88
6	4-(BocO)Ph (**5f**)	Me	82 (**6f**)	94
7	4-(CN)Ph (**5g**)	Me	92 (**6g**)	98
8	3-(MeO)Ph (**5h**)	Me	95 (**6h**)	88
9	3-ClPh (**5i**)	Me	96 (**6i**)	88
10	1-naphthyl (**5j**)	Me	86 (**6j**)	90
11	2-(MeO)Ph (**5k**)	Me	85 (**6k**)	70
12	2-ClPh (**5l**)	Me	93 (92[d]) (**6l**)	56 (84[d])
13	1-thiophyl (**5m**)	Me	91 (**6m**)	82
14	2-furyl (**5n**)	Me	93 (**6n**)	74
15	*i*-Pr (**5o**)	Me	95 (**6o**)	46
16	Et (**5p**)	Me	89 (**6p**)	45
17	4-BrPh (**5c**)	H	71 (**6q**)	81
18	4-BrPh (**5c**)	n-C_4H_9	88 (**6r**)	92
19	4-BrPh (**5c**)	Ph	81 (**6s**)	92
20	4-BrPh (**5c**)	*t*-Bu	85 (**6t**)	86
21	4-BrPh (**5c**)	TMS	89 (**6u**)	81
22	4-BrPh (**5c**)	Me	96 (**6v**)	−91[e]

[a] Isolated yields after chromatography. [b] Determined by chiral HPLC. [c] After one crystallization from acetone/water. [d] Using 1.9 equiv of (*rac*)-Mosher acid instead of CF_3CH_2OH. [e] Using cinchonine as the chiral ligand instead of cinchonidine to obtain the opposite enantiomer of the product.

considerably affect the reaction efficiency (82−96% yield) or asymmetric induction (88−98% ee). Although ortho-substituted arene acceptors (entries 11 and 12) and aliphatic acceptors (entries 15 and 16) generally provided moderate ee (45−70%), this limitation could be overcome by use of (*rac*)-Mosher acid instead of trifluoroethanol as the additive (entry 12). The process was also suitable for heterocyclic substrates, such as furyl and thiophyl (entries 13 and 14). A wide variety of Zn alkynylides, including those possessing aliphatic, aromatic, and silyl groups, could be employed in the conjugate addition with high ee (entries 17−22). Remarkably, even with the smallest alkynyl nucleophile (derived from acetylene), 81% ee and 71% yield were achieved (entry 17). Importantly, all of the starting materials **5** and products **6** were crystalline, allowing simple isolations and ee upgrades by crystallization (entries 1 and 3).

In summary, we have developed a highly general, practical asymmetric alkynylation procedure for the preparation of β-alkynyl acids. These results demonstrate for the first time that unactivated aliphatic alkynes (even acetylene) can be employed in the enantioselective conjugate alkynylation of ester-derived acceptors to afford products in both high yield and enantioselectivity. The inexpensive and recyclable chiral mediator cinchonidine, crystalline nature of the starting materials and products, excellent functional group compatibility of the process, wide substrate scope, and ability to prepare either enantiomer of the product (Table 2, entry 22) make this an attractive new synthetic method.

Acknowledgment. We are grateful to Dr. Tsang-Lin Hwang for NMR structural work.

Supporting Information Available: Experimental procedures and spectral data for all new compounds and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) A variety of other chiral ligands and metals, including copper, rhodium, and lithium, were also evaluated, but they afforded lower yields and enantioselectivities.

(6) The method used to generate the chiral alkynylzinc reagents played a key role. Chiral alkynylzinc reagents produced by transmetalation provided superior reactivity to in situ-generated chiral zinc alkynylides obtained using Zn^{II}/R_3N. See the Supporting Information for detailed optimization work.

(7) The absolute configuration was determined by single-crystal X-ray crystallographic analysis. See the Supporting Information.

(8) For similar zinc species, see: (a) Enders, D.; Zhu, J.; Raabe, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 1725. (b) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (c) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934. (d) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. *J. Angew. Chem., Int. Ed.* **1999**, *38*, 711.

(9) Ultimately, trifluoroethanol was selected for further optimization studies because of its low cost and easy removal by distillation.

(10) No reaction was detected below −30 °C, and reactions at 0 and 30 °C gave 92 and 88% ee, respectively.

(11) (a) Reactions were slower in the absence of trifluoroethanol. For example, the reaction in Table 1, entry 1, reached 100% conversion in <6 h at rt. When the reaction was performed with 4.8 equiv of cinchonidine (no CF_3CH_2OH) at rt for 24 h, 93% conversion and 94% ee was observed. (b) Other evaluated solvents (Me-THF, MTBE, DME, toluene) provided lower ee (<80%) and yield (<90%). (c) Me_2Zn and Et_2Zn were equally efficient. (d) The enantioselectivity was not dependent on the concentration (0.04−0.2 M). (e) The order of addition of reagents during the zincate preparation had no effect.

(12) In Scheme 1, zincate **4** is depicted as a monomer for clarity. Preliminary NMR studies indicate that several different zincate species exist in solution.

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