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Enantioselective Iridium-Catalyzed Vinylogous Reformatsky-Aldol Reaction from the Alcohol Oxidation Level: Linear Regioselectivity by Way of Carbon-Bound Enolates**

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aldol reaction; allylation; homogeneous catalysis; iridium; transfer hydrogenation

Vinylogues^[1] of the aldol reaction represent an important class of carbonyl addition processes.^[2] The vast majority of enantioselective vinylogous aldol additions employ dienolates and dienol ethers derived from β -ketoesters^[3] in combination with chiral Lewis acids,^[3a–k] chiral Lewis bases,^[3k–m] or chiral hydrogen-bond donors.^[3n] Dienolates and dienol ethers derived from simple α,β -unsaturated carbonyl compounds^[3k–m,4] and 2-siloxy furans^[5] also participate in enantioselective vinylogous aldol additions. While excellent regio- and enantioselectivities have been obtained in certain cases, the formation and tractability of the requisite dienol ethers pose a barrier to their use. Additionally, chiral Lewis acid catalyzed reactions of silyl dienol ethers often suffer from competing racemic silyl cation catalyzed background reactions, thus requiring slow addition of the dienol ether, cryogenic conditions, and high catalyst loadings. Vinylogous direct aldol additions of unmodified unsaturated carbonyl compounds potentially address these limitations,^[6] however, to date, such transformations are restricted to the use of 2-(5*H*)-furanones or nitriles as aldol donors.^[6,7]

In a significant departure from prior art, Kanai, Shibasaki, and co-workers devised a reductive vinylogous aldol reaction of allenic esters mediated by pinacolborane.^[8] A related reductive process, the vinylogous Reformatsky reaction, could potentially deliver identical products, however, enantioselective variants are unknown.^[9] Herein, under the conditions of C–C bond-forming transfer hydrogenation,^[10,11] we report the first examples of enantioselective vinylogous Reformatsky-type additions, and establish catalytic conditions wherein asymmetric carbonyl addition occurs with equal facility from the alcohol or aldehyde oxidation level (Scheme 1).

In recent work, our research group has found that chiral *ortho*-cyclometalated iridium C,O-benzoates catalyze carbonyl allylation,^[10a,b,e–h] crotylation,^[10c,f] *tert*-prenylation,^[10d,f] and a host of related carbonyl allylation processes. For such “C–C bond-forming transfer hydrogenations”^[10,11] secondary alcohol dehydrogenation triggers reductive generation of

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allyliridium nucleophiles, which, in the presence of exogenous aldehyde, deliver products of carbonyl allylation. Of greater significance, primary alcohol dehydrogenation can simultaneously generate aldehyde–allyliridium pairs, thus enabling carbonyl addition from the alcohol oxidation level. For all reactions that occur by way of substituted π -allyl iridium intermediates, complete branched regioselectivities are accompanied by good to complete levels of *anti*-diastereoselectivity, thus suggesting carbonyl addition occurs with allylic inversion from the primary (*E*)- σ -allyl haptomer. To date, the formation of linear carbonyl addition products from substituted allyliridium nucleophiles has proven elusive (Scheme 2).

It was reasoned that linear carbonyl addition products might be availed upon stabilization of the secondary σ -allyl haptomer through introduction of a carbonyl moiety, in which case the secondary σ -allyl haptomer is equivalent to an η^1 -C-bound iridium enolate.^[12] The veracity of this analysis is borne out by the following experiments. Upon exposure of the γ -acyloxy crotonate **1** to primary alcohol **2a** in the presence of the chiral *ortho*-cyclometalated iridium C,O-benzoate complex modified by (*R*)-Cl, MeO-biphep, (2,2'-bis(diphenylphosphino)-5,5'-dichloro-6,6'-dimethoxy-1,1'-biphenyl), designated (*R*)-**I**, the products of carbonyl addition were obtained in a combined 87% yield as a 1:2 mixture of linear (88% *ee*) and branched regioisomers, thus favoring formation of the branched adduct, which appeared as a roughly equimolar mixture of diastereomers (Table 1, entry 1). Catalytic C–C coupling of cyclopentanemethanol **2b** or cyclohexanemethanol **2c** under identical conditions revealed an increased proportion of the linear regioisomer (approximately 5:1 r.r. in each case), again accompanied by high levels of enantioselectivity (94% *ee* and 95% *ee*, respectively; Table 1, entries 2 and 3). Primary neopentyl alcohols **2d–2h** delivered products of C–C coupling with complete linear regioselectivity and exceptional enantioselectivity (Table 1, entries 4–8). In all cases, roughly equivalent yields and selectivities are observed when the C–C coupling was performed using aldehydes **3a–3h** (Table 2, entries 1–8). Finally, benzylic alcohols **2i** and **2j** and the corresponding aldehydes **3i** and **3j** engage in C–C coupling to furnish adducts **4i** and **4j** (Table 1, entries 9 and 10 and Table 2, entries 9 and 10, respectively). A detailed description of the assignment of absolute stereochemistry is provided in the Supporting Information.

Linear regioselectivity in response to increased steric demand of the aldehyde suggests a Curtin–Hammett scenario wherein carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ -allyl haptomers.^[13,14] Beyond electronic effects, it is likely that carbonyl addition from the α -C-bound iridium enolate to form the less-substituted C–C bond is favored owing to the absence of gauche interactions in the transition state. For sterically demanding aldehydes, such gauche interactions would be accentuated, thus increasing the preference for the linear regioisomer (Scheme 3).

To further explore the scope of the vinylogous Reformatsky–aldol addition, catalyst-directed diastereoselectivity was explored in the coupling of allylic carbonate **1** to α -chiral alcohol **2k** (Scheme 4).^[15] Under standard conditions employing (*R*)-**I** as the precatalyst, the linear adduct **4k** was isolated as a single regio- and stereoisomer. Using the enantiomeric precatalyst (*S*)-**I**, the linear adduct *epi*-**4k** was isolated as a single regio- and stereoisomer. Thus, complete levels of catalyst-directed diastereoselectivity are observed.^[16] In contrast, using the analogous achiral iridium complex modified by biphep, (2,2'-bis(diphenylphosphino)biphenyl), diastereomers **4k** and *epi*-**4k** were produced in 58% yield in a 1:1.5 ratio, respectively, along with a 9% yield of the branched regioisomer. It should be noted that although biphep is considered an achiral ligand, metal complexes of biphep adopt chiral racemic conformations that would attenuate substrate bias.

In summary, a catalytic enantioselective vinylogous Reformatsky-type addition has been described in which asymmetric carbonyl addition occurs with equal facility from the alcohol

or aldehyde oxidation level. Good to excellent levels of regioselectivity and uniformly high levels of enantioselectivity are observed across a range of alcohols **2a–2i** and aldehydes **3a–3i**. Furthermore, as demonstrated in the case of α -chiral alcohol **2k**, exceptional levels of catalyst-directed diastereoselectivity may be achieved. Insight into the structure–interaction features of the catalytic system vis-à-vis partitioning of linear and branched adducts suggests a Curtin–Hammett scenario, wherein carbonyl addition occurs selectively from an equilibrating mixture of primary and secondary σ -allyl haptomers.^[13,14] The collective data are consistent with carbonyl addition from the secondary α -C-bound iridium enolate to form the less-substituted C–C bond owing to the absence of gauche interactions in the transition state. Notably, in reactions conducted from the alcohol oxidation level, the only stoichiometric by-products formed are carbon dioxide and *tert*-butanol. Future studies will focus on the development of related C–C bond-forming processes that combine oxidation/construction event and thus bypass discrete alcohol oxidation and stoichiometric organometallic reagents while gaining access to more tractable synthetic intermediates in the form of alcohols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Fuson RC. *Chem Rev.* 1935; 16:1–27.
2. For selected reviews on the vinylogous aldol reaction, see: a) Casiraghi G, Zanardi F. *Chem Rev.* 2000; 100:1929–1972. [PubMed: 11749280] b) Soriente A, De Rosa M, Villano R, Scettri A. *Curr Org Chem.* 2004; 8:993–1007. c) Denmark SE, Heemstra JR Jr, Beutner GL. *Angew Chem.* 2005; 117:4760–4777. *Angew Chem Int Ed.* 2005; 44:4682–4698. d) Kalesse M. *Top Curr Chem.* 2005; 244:43–76. e) Hosokawa S, Tatsuta K. *Mini-Rev Org Chem.* 2008; 5:1–18. f) Zanardi F, Battistini L, Curti C, Casiraghi G, Rassa G. *Chemtracts: Org Chem.* 2010; 23:123–140.
3. For examples of enantioselective vinylogous aldol reactions of β -ketoester derived dienols and dienolates, see: a) Sato M, Sunami S, Sugita Y, Kaneko C. *Chem Pharm Bull.* 1994; 42:839–845. b) Singer RA, Carreira EM. *J Am Chem Soc.* 1995; 117:12360–12361. c) Sato M, Sunami S, Sugita Y, Kaneko C. *Heterocycles.* 1995; 41:1435–1444. d) De Rosa M, Acocella MR, Villano R, Soriente A, Scettri A. *Tetrahedron Lett.* 2003; 44:6087–6090. e) Villano R, Acocella MR, De Rosa M, Soriente A, Scettri A. *Tetrahedron: Asymmetry.* 2004; 15:2421–2424. f) Evans DA, Murry JA, Kozlowski MC. *J Am Chem Soc.* 1996; 118:5814–5815. g) Evans DA, Kozlowski MC, Murry JA, Burgey CS, Campos KR, Connell BT, Staples RJ. *J Am Chem Soc.* 1999; 121:669–685. h) Krüger J, Carreira EM. *J Am Chem Soc.* 1998; 120:837–838. i) Pagenkopf BL, Krüger J, Stojanovic A, Carreira EM. *Angew Chem.* 1998; 110:3312–3314. *Angew Chem Int Ed.* 1998; 37:3124–3126. j) Shimada Y, Matsuoka Y, Irie R, Katsuki T. *Synlett.* 2004; 57–60. k) Denmark SE, Beutner GL. *J Am Chem Soc.* 2003; 125:7800–7801. [PubMed: 12822988] l) Denmark SE, Beutner GL, Wynn T, Eastgate MD. *J Am Chem Soc.* 2005; 127:3774–3789. [PubMed: 15771512] m) Denmark SE, Heemstra JR Jr. *J Org Chem.* 2007; 72:5668–5686. [PubMed: 17583959] n) Gondi VB, Gravel M, Rawal VH. *Org Lett.* 2005; 7:5657–5660. [PubMed: 16321015] o) Yoshinari T, Ohmori K, Suzuki K. *Chem Lett.* 2010; 39:1042–1044.
4. For examples of enantioselective vinylogous aldol reactions of dienols and dienolates derived from simple α,β -unsaturated carbonyl compounds, see: a) Bluet G, Campagne JM. *Tetrahedron Lett.* 1999; 40:5507–5509. b) Bluet G, Campagne JM. *J Org Chem.* 2001; 66:4293–4298. [PubMed: 11397166] c) Bazán-Tejeda B, Bluet G, Broustal G, Campagne JM. *Chem Eur J.* 2006; 12:8358–8366. d) Denmark SE, Heemstra JR Jr. *Synlett.* 2004; 2411–2416. e) Moreau X, Bazán-Tejeda B, Campagne JM. *J Am Chem Soc.* 2005; 127:7288–7289. [PubMed: 15898758] f) Denmark SE, Heemstra JR Jr. *J Am Chem Soc.* 2006; 128:1038–1039. [PubMed: 16433495] g) Rémy P, Langner M, Bolm C. *Org Lett.* 2006; 8:1209–1211. [PubMed: 16524305] h) Heumann LV, Keck GE. *Org Lett.* 2007; 9:4275–4278. [PubMed: 17887693] i) Simsek S, Horzella M, Kalesse M. *Org Lett.* 2007; 9:5637–5639. [PubMed: 18052187] j) Fings M, Goedert D, Bolm C. *Chem Commun.* 2010;

- 46:5497–5499.k) Ratjen L, Garcia-Garcia P, Lay F, Beck ME, List B. *Angew Chem*. 2011; 123:780–784. *Angew Chem Int Ed*. 2011; 50:754–758.
5. For examples of enantioselective vinylogous aldol reactions of 2-siloxy furan and 2-siloxy pyrrole, see: a) Szlosek M, Franck X, Figadère B, Cavé A. *J Org Chem*. 1998; 63:5169–5172.b) Matsuoka Y, Irie R, Katsuki T. *Chem Lett*. 2003; 32:584–585.c) Onitsuka S, Matsuoka Y, Irie R, Katsuki T. *Chem Lett*. 2003; 32:974–975.d) Nagao H, Yamane Y, Mukaiyama T. *Chem Lett*. 2007; 36:8–9.e) Frings M, Atodiressei I, Runsink J, Raabe G, Bolm C. *Chem Eur J*. 2009; 15:1566–1569.f) Curti C, Sartori A, Battistini L, Rassu G, Zanardi F, Casiraghi G. *Tetrahedron Lett*. 2009; 50:3428–3431.g) Singh RP, Foxman BM, Deng L. *J Am Chem Soc*. 2010; 132:9558–9560. [PubMed: 20583835]
 6. For “direct” enantioselective vinylogous aldol additions of unsaturated carbonyl compounds and nitriles, see: a) Ube H, Shimada N, Terada M. *Angew Chem*. 2010; 122:1902–1905. *Angew Chem Int Ed*. 2010; 49:1858–1861.b) Yang Y, Zheng K, Zhao J, Shi J, Lin L, Liu X, Feng X. *J Org Chem*. 2010; 75:5382–5384. [PubMed: 20590136] c) Yazaki R, Kumagai N, Shibasaki M. *J Am Chem Soc*. 2010; 132:5522–5531. [PubMed: 20337453]
 7. For a related vinylogous aldol-oxa-Michael cascade reaction, see: Liu K, Woggon WD. *Eur J Org Chem*. 2010:1033–1036.
 8. Zhao D, Oisaki K, Kanai M, Shibasaki M. *J Am Chem Soc*. 128:2006. 14440–14441.
 9. For the seminal report of the vinylogous Reformatsky-type reaction, see: a) Fuson RC, Arnold RT, Cooke HG Jr. *J Am Chem Soc*. 1938; 60:2272–2273.b) Fuson RC, Southwick PL. *J Am Chem Soc*. 1944; 66:679–681.
 10. For enantioselective carbonyl allylation by iridium-catalyzed C–C bond-forming transfer hydrogenation and related processes, see: a) Kim IS, Ngai MY, Krische MJ. *J Am Chem Soc*. 2008; 130:6340–6341. [PubMed: 18444616] b) Kim IS, Ngai MY, Krische MJ. *J Am Chem Soc*. 2008; 130:14891–14899. [PubMed: 18841896] c) Kim IS, Han SB, Krische MJ. *J Am Chem Soc*. 2009; 131:2514–2520. [PubMed: 19191498] d) Han SB, Kim IS, Han H, Krische MJ. *J Am Chem Soc*. 2009; 131:6916–6917. [PubMed: 19453190] e) Lu Y, Kim IS, Hassan A, Del Valle DJ, Krische MJ. *Angew Chem*. 2009; 121:5118–5121. *Angew Chem Int Ed*. 2009; 48:5018–5021.f) Itoh J, Han SB, Krische MJ. *Angew Chem*. 2009; 121:6431–6434. *Angew Chem Int Ed*. 2009; 48:6313–6316.g) Lu Y, Krische MJ. *Org Lett*. 2009; 11:3108–3111. [PubMed: 19586066] h) Hassan A, Lu Y, Krische MJ. *Org Lett*. 2009; 11:3112–3115. [PubMed: 19586067] i) Bechem B, Patman RL, Hashmi S, Krische MJ. *J Org Chem*. 2010; 75:1795–1798. [PubMed: 20131774] j) Han SB, Han H, Krische MJ. *J Am Chem Soc*. 2010; 132:1760–1761. [PubMed: 20099821] k) Zhang YJ, Yang JH, Kim SH, Krische MJ. *J Am Chem Soc*. 2010; 132:4562–4563. [PubMed: 20225853] l) Han SB, Gao X, Krische MJ. *J Am Chem Soc*. 2010; 132:9153–9156. [PubMed: 20540509] m) Zbieg JR, Fukuzumi T, Krische MJ. *Adv Synth Catal*. 2010; 352:2416–2420. [PubMed: 21165157] for recent applications in total synthesis, see: n) Harsh P, O’Doherty GA. *Tetrahedron*. 2009; 65:5051–5055. [PubMed: 20161297] o) Han SB, Hassan A, Kim IS, Krische MJ. *J Am Chem Soc*. 2010; 132:15559–15561. [PubMed: 20961111] p) Sawant P, Maier ME. *Tetrahedron*. 2010; 66:9738–9744.
 11. For selected reviews on C–C bond-forming hydrogenation and transfer hydrogenation, see: a) Ngai MY, Kong JR, Krische MJ. *J Org Chem*. 2007; 72:1063–1072. [PubMed: 17288361] b) Skucas E, Ngai MY, Komanduri V, Krische MJ. *Acc Chem Res*. 2007; 40:1394–1410. [PubMed: 17784728] c) Shibahara F, Krische MJ. *Chem Lett*. 2008; 37:1102–1107.d) Patman RL, Bower JF, Kim IS, Krische MJ. *Aldrichim Acta*. 2008; 41:95–104.e) Bower JF, Kim IS, Patman RL, Krische MJ. *Angew Chem*. 2009; 121:36–48. *Angew Chem Int Ed*. 2009; 48:34–46.f) Han SB, Kim IS, Krische MJ. *Chem Commun*. 2009:7278–7287.g) Bower JF, Krische MJ. *Top Organomet Chem*. 2011; 43:107–138. [PubMed: 21822399]
 12. For reviews covering the coordination chemistry of late-transition-metal enolates, including their η^1 -C-bound haptomers, see: a) Burkhardt ER, Doney JJ, Sough GA, Stack JM, Heathcock CH, Bergman RG. *Pure Appl Chem*. 1988; 60:1–6.b) Vicente J, Zabicky J. *The Chemistry Of Metal Enolates*. WileyChichester2009:313–353.
 13. Such Curtin–Hammett effects appear evident in Nozaki–Hiyama crotylation reactions: a) Hiyama T, Okude Y, Kimura K, Nozaki H. *Bull Chem Soc Jpn*. 1982; 55:561–568.b) Roush WR, Trost BM, Fleming I, Heathcock CH. *Comprehensive Organic Synthesis*. 2PergamonOxford1991; :1–53.

14. For Curtin–Hammett effects in ruthenium-catalyzed carbonyl addition reactions involving 1,1-disubstituted allenes as allyl donors, see: Zbieg JR, McInturff EL, Leung JC. *J Am Chem Soc.* 2011; 133:1141–1144. [PubMed: 21175178]
15. Alcohol 2k was prepared by Sharpless asymmetric dihydroxylation according to the following literature procedure: Wright BJD, Hartung J, Peng F, Van der Water R, Liu H, Tan QH, Chou TC, Danishefsky SJ. *J Am Chem Soc.* 2008; 130:16786–16790. [PubMed: 19049469]
16. For selected examples of catalyst-directed diastereoselectivity, see: a) Minami N, Ko SS, Kishi Y. *J Am Chem Soc.* 1982; 104:1109–1111. b) Ko SY, Lee AWM, Masamune S, Reed LA III, Sharpless KB, Walker FJ. *Science.* 1983; 220:949–951. [PubMed: 17816019] c) Kobayashi S, Ohtsubo A, Mukaiyama T. *Chem Lett.* 1991:831–834. d) Hammadi A, Nuzillard JM, Poulin JC, Kagan HB. *Tetrahedron: Asymmetry.* 1992; 3:1247–1262. e) Doyle MP, Kalinin AV, Ene DG. *J Am Chem Soc.* 1996; 118:8837–8846. f) Trost BM, Calkins TL, Oertelt C, Zambrano J. *Tetrahedron Lett.* 1998; 39:1713–1716. g) Balskus EP, Jacobsen EN. *Science.* 2007; 317:1736–1740. [PubMed: 17885133] h) Han SB, Kong JR, Krische MJ. *Org Lett.* 2008; 10:4133–4135. [PubMed: 18729371]

Catalytic Enantioselective Processes - Known **Catalytic Enantioselective Processes - Unknown** **Scheme 1.**

Catalytic enantioselective vinylogous aldol reactions. PG = protecting group.

Scheme 2.

Carbonyl addition by way of primary σ -allyl haptomers typically generates branched products as *anti*-diastereomers.

Scheme 3.
Partitioning of branched and linear regioisomers.

Scheme 4.

Catalyst-directed diastereoselectivity in vinylogous Reformatsky–aldol addition from the alcohol oxidation level.

Table 1Enantioselective vinylogous Reformatsky reaction from the alcohol oxidation level.^[a]

Entry	Product	Yield [%]	<i>ee</i> [%]	γ/α
1		87	88	1:2
2		74	94	5:1
3		77	95	5:1
4		59	96	$\geq 20:1$
5		88	96	$\geq 20:1$
6		75	99	$\geq 20:1$
7		70	97	$\geq 20:1$
8		61	90	$\geq 20:1^{[b]}$
9		80	86	$\geq 20:1$
10		80	95	5:1

^[a]Yields are of isolated product. Enantiomeric excess was determined by HPLC on a chiral stationary phase. See the Supporting Information for further details.

^[b]24 h. Boc = *tert*-butoxycarbonyl, PMB = *para*-methoxybenzyl, Ts = 4-toluenesulfonyl.

Table 2Enantioselective vinylogous Reformatsky reaction from the aldehyde oxidation level.^[a]

Entry	Product	Yield [%]	<i>ee</i> [%]	γ/a
1		65	83	1:2 ^[b]
2		80	98	6:1
3		88	92	6:1
4		85	96	≥ 20:1
5		70	99	≥ 20:1
6		83	99	≥ 20:1
7		60	93	≥ 20:1
8		58	93	≥ 20:1
9		80	94	≥ 20:1
10		94	96	5:1

^[a] As described in Table 1.