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Enantio-, Diastereo- and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic β-Ketoesters

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Abstract

The first regio-, diastereo- and enantioselective allylic alkylation of acyclic β-ketoesters to form vicinal tertiary and all-carbon quaternary stereocenters is reported. Critical to the successful development of this method was the employment of iridium catalysis in concert with *N*-aryl-phosphoramidite ligands. Broad functional group tolerance is observed at the keto-, ester-, and α-positions of the nucleophile. Various transformations demonstrating the utility of this method for rapidly accessing complex enantioenriched compounds are reported.

The enantioselective synthesis of all-carbon quaternary stereocenters is an enduring challenge faced by organic chemists and a subject of longstanding interest in our laboratory.[1, 2] The generation of enantioenriched all-carbon quaternary centers is complicated by the presence of vicinal tertiary stereocenters due to increased steric demands and the introduction of requisite diastereocontrol. Modern strategies for accessing these highly congested stereochemical dyads have relied primarily on transition metal catalysis,[3–7] notably Pd-catalyzed enolate alkylation cascades,[3] Pd-catalyzed trimethylenemethane cycloadditions, [4] Cu-catalyzed asymmetric Claisen rearrangements,[5] and Mo[6]- and Ir[7]-catalyzed allylic alkylations. Common to the majority of these reports is the constraint that the nascent quaternary center be formed at a cyclic nucleophile. To date, only two groups have reported success in employing linear nucleophiles to produce vicinal quaternary/tertiary arrays. Namely, Trost's communication on the molybdenum-catalyzed allylic alkylation of β-cyanoesters[6b] and Carreira's recent report on the allylic alkylation of aldehydes using stereodivergent dual catalysis.[7a] To address these limitations, we have initiated studies investigating the asymmetric allylic alkylation of linear β-ketoesters.

Recently, our group demonstrated the power of iridium-*N*-arylphosphoramidite catalysis [8] in accessing vicinal all-carbon quaternary and tertiary stereocenters with our report on the regio-, diastereo- and enantioselective asymmetric allylic alkylation of cyclic β-ketoesters (Scheme 1a).[7b, 9, 10] The success of this protocol combined with the virtual absence of reports describing the application of this transformation to acyclic β-ketoesters encouraged our further exploration of iridium catalysts in the domain of this important substrate class. Herein, we report the first highly regio-, diastereo- and enantioselective allylic alkylation of acyclic β-ketoesters to forge vicinal tertiary, quaternary centers (Scheme 1b).

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ASSOCIATED CONTENT

Experimental procedures, characterization data, X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

Having chosen ethyl 2-methyl-3-oxo-3-phenylpropanoate (**1a**) and cinnamyl carbonate (**2a**) as standard coupling partners, several iridacycle complexes [11] were investigated at the outset of our studies as shown in Table 1 (entries 1–6). We found that exposure of standard substrates (**1a**) and (**2a**) to a combination of catalytic phosphoramidite ligand **L1**•$[Ir(cod)Cl]_2$ complex[12] and two equiv NaH in THF at ambient temperature afforded the desired product with good conversion, ee and regioselectivity but low levels of diastereoselectivity (1:2) (entry 1). Use of either **L2** or **L4** under these conditions instead favored the reaction pathway yielding the undesired, linear allylic alkylation product in modest conversion (entries 2 and 4). Ligands **L5** and **L6**[8b, 13] gave the branched product in good conversion but with diminished diastereoselectivity and enantioselectivity and protracted reaction times (entries 5 and 6). We were pleased to find that tetrahydroquinoline based ligand **L3**[8] rapidly furnished the desired α-quaternary β-ketoester (**3a**) in greater than 95% conversion, 95:5 regioselectivity, 13:1 dr and 99% enantiomeric excess (entry 3). Previous reports demonstrating the marked effect of metal cations over regio-[14] and diastereoselectivity[7b,10e] in iridium-catalyzed allylic alkylations prompted further investigation of both bases and additives (see SI for details). Contrary to our previous findings,[7b] a sluggish reaction was observed when LiBr was used in place of NaH (entry 7), presumably due to the decreased α-acidity of acyclic β-ketoesters relative to cyclic substrates. Use of alkoxide bases in place of NaH, however, resulted in considerably reduced reaction times (entries 8–9). The dramatically diminished diastereoselectivity with KO*t*-Bu, Cs_2CO_3, and DABCO indicates that the presence of lithium cation in the reaction has a pronounced influence over the diastereoselectivity, likely due to formation of a rigid, bidentate-chelated lithium enolate ester (entries 8–11). Ultimately, it was found that LiO*t*-Bu proved optimal, delivering β-ketoester **3a** with an exceptional branched to linear ratio (93:7), >20:1 diastereoselectivity, and 98% enantioselectivity in only two hours (entry 8).

With optimized conditions identified, the scope of the reaction with respect to the electrophile was next explored. A highly selective reaction was observed between β-ketoester **1a** and various cinnamyl carbonate-derived electrophiles (**2**) bearing electron-donating substitutents about the aryl group, R (Table 2, entries 2–4). 4-Me-, 4-MeO-, and 3-MeO-substitutions about the aryl ring (substrates **2b–2d**) gave the corresponding α-quaternary β-ketoesters (products **3b–3d**) in good to excellent yield, dr, ee and branched to linear ratio (Table 2). Electron deficient aryl substituents at the allyl group (entries 5–7) were also well tolerated, delivering the branched products **3e–3g**[15] in good to excellent yields, outstanding ee and dr, and with only slightly diminished regioselectivities. Interestingly, (4-nitro)-aryl substitution at the allyl carbonate (entry 8, substrate **2h**) led to loss of regioselectivity in the reaction, giving equal amounts of products **3h** (14:1 dr, 93% ee) and **4h** (23% ee). We were pleased to discover, however, that heteroaryl-substituted allyl carbonates (substrates **2i** and **2j**) resulted in smooth reactions and delivered alkylated products **3i** and **3j** with excellent yield, ee and regioselectivity and with good to excellent dr (entries 9–10). Finally, we found that sorbyl carbonate **2k** was also a suitable participant in the reaction, giving the corresponding product (**3k**) in good yield and dr and with excellent regio- and enantioselectivities (entry 11).

During the course of this investigation, a trend relating regioselectivity and electrophile electron deficiency began to emerge. Specifically, the regioselectivity of the reaction diminished as the electron deficiency of the cinnamyl substituent increased. In order to identify any linear free energy relationship governing the reaction, we performed a linear relationship analysis relating the log of the ratio of branched to linear products, which is proportional to the relative rates of product formation, to the corresponding Brown σ^+ constants.[16,17] The negative ρ value observed from this plot suggests that as the magnitude of electropositive charge generated at the putative cinnamyl-Ir intermediate [18] increases, the reaction pathway yielding the branched allylation product becomes more favorable. [19]

Having investigated reaction substrate scope with respect to the allyl electrophile, we next examined the diversity of nucleophilic coupling partners permitted in the chemistry (Table 3). β-Ketoesters (**1**) bearing either electron-donating or electron-withdrawing aryl substituents (R^1) at the ketone fared very well in the reaction, delivering products **3l** and **3m** in excellent yield, dr, ee and branched to linear ratio (entries 1 and 2). Gratifyingly, a wide variety of functional groups are readily permitted at the α-position (R^2), including alkyl, benzyl, allyl, propargyl, keto and heteroaryl groups (substrates **1n–1s**, entries 3–8, respectively). The products of these reactions (products **3n–3s**, respectively) were obtained with excellent ee and regioselectivities and in good to excellent dr and yield. To the best of our knowledge, substrate **1q** represents the first example of nucleophile bearing propargyl substitution to undergo Ir-catalyzed allylic substitutions. [20] Nitrile-containing substituents were tolerated in the reaction as well (substrate **1t**), and α- quaternary β-ketoester **3t** was furnished in excellent yield, ee and regioselectivity, albeit with diminished dr (3:1). We were pleased to learn that use of α-halogenated nucleophiles (substrates **1u** and **1v**) also resulted in an efficient and selective reaction as α-fluoro and α-chloro β-ketoesters **3u** and **3v** were obtained in excellent yields, dr, ee and regioselectivity. In addition to aryl ketones, cyclohexenyl β-ketoester **1w** was found to deliver the corresponding product **3w** in excellent yield, dr, ee and branched to linear ratio with no detectable products resulting from competitive bimolecular Michael addition. Although the use of alkyl β-ketoesters **1x** and **1y** provided the desired products (**3x** and **3y**, respectively) with excellent yields, ee and regioselectivites, we were disappointed to find that the diastereoselectivities were diminished considerably. Lastly, we found that the use of a sterically hindered ester moiety (**1z**) gave an efficient and highly enantioselective reaction but with a concurrent loss in regio- and diastereoselectivity (entry 15).

In order to exhibit the utility of our method for generating interesting and useful chiral building blocks, a number of selective transformations were carried out on products obtained in the course of our studies (Scheme 2). Aldol condensation of β-ketoester **3r** yielded γ-quaternary cyclohexenone **5**. Pauson–Khand cyclization of progaryl-substituted β-ketoester **3q** smoothly delivered bicycle **6**.[20b] Finally, ring closing metathesis of diallyl β-ketoester **3p** cleanly furnished cyclohexene **7**.

In summary, the first enantioselective catalytic allylic alkylation of linear β-ketoesters to generate vicinal quaternary and tertiary stereocenters in high yield, dr, ee and regioselectivity has been reported. The process hinges on the use of an Ir•*N*-aryl-phosphoramidite catalyst. A variety of substitution patterns at the allyl electrophile and β-ketoester are well tolerated in the chemistry. A number of transformations were carried out on reaction products to demonstrate the value this method holds for the rapid generation of highly functionalized chiral building blocks. Studies utilizing this method toward the synthesis of complex biologically active natural products are underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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REFERENCES

1. For selected reviews, see: Douglas CJ, Overman LE. Proc. Natl. Acad. Sci. U.S.A.. 2004; 101:5363. [PubMed: 14724294] Christoffers J, Baro A. Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis. 2005WeinheimWiley-VCH Trost BM, Jiang C. Synthesis. 2006:369. Das JP, Marek I. Chem. Commun.. 2011; 47:4593.
2. (a) Mohr JT, Stoltz BM. Chem. Asian J.. 2007; 2:1476. [PubMed: 17935094] (b) Behenna DC, Stoltz BM. J. Am. Chem. Soc.. 2004; 126:15044. [PubMed: 15547998] (c) Mohr JT, Behenna DC, Harned AM, Stoltz BM. Angew. Chem., Int. Ed.. 2005; 44:6924.(d) Behenna DC, Mohr JT, Sherden NH, Marinescu SC, Harned AM, Tani K, Seto M, Ma S, Novák Z, Krout MR, McFadden RM, Roizen JL, Enquist JA Jr, White DE, Levine SR, Petrova KV, Iwashita A, Virgil SC, Stoltz BM. Chem. – Eur. J.. 2011; 17:14199. [PubMed: 22083969] (e) Behenna DC, Liu Y, Yurino T, Kim J, White DE, Virgil SC, Stoltz BM. Nature Chem.. 2012; 4:130. [PubMed: 22270628]
3. Streuff J, White DE, Virgil SC, Stoltz BM. Nature Chem.. 2010; 2:192. [PubMed: 20697457]
4. (a) Trost BM, Cramer N, Silverman SM. J. Am. Chem. Soc.. 2007; 129:12396. [PubMed: 17880222] (b) Trost BM, Silverman SM, Stambuli JP. J. Am. Chem. Soc.. 2011; 133:19483. [PubMed: 21936576]
5. Tan J, Cheon C-H, Yamamoto H. Angew. Chem. Int. Ed.. 2012; 51:8264.
6. (a) Trost BM, Zhang Y. Am. Chem. Soc.. 2007; 129:14548.(b) Trost BM, Miller JR, Hoffman CM Jr. J. Am. Chem. Soc.. 2011; 133:8165. [PubMed: 21534526]
7. (a) Krautwald S, Sarlah D, Schafroth MA, Carreira EM. Science. 2013; 340:1065. [PubMed: 23723229] (b) Liu W-B, Reeves CM, Virgil SC, Stoltz BM. J. Am. Chem. Soc.. 2013; 135:10626. [PubMed: 23829704]
8. (a) Liu W-B, He H, Dai L-X, You S-L. Synthesis. 2009:2076.(b) Liu W-B, Zheng C, Zhuo C-X, Dai L-X, You S-L. J. Am. Chem. Soc.. 2012; 134:4812. [PubMed: 22309279]
9. For the first example: Takeuchi R, Kashio M. Angew. Chem. Int. Ed. Engl.. 1997; 36:263. Janssen JP, Helmchen G. Tetrahedron Lett. 1997; 38:8025. For reviews: Helmchen G, Dahnz A, Dübon P, Schelwies M, Weihofen R. Chem. Commun. 2007:675. Helmchen G. Oro LA, Claver C. Iridium Complexes in Organic Synthesis. 2009Weinheim, GermanyWiley-VCH:211. Hartwig JF, Pouy MJ. Top. Organomet. Chem. 2011; 34:169. Tosatti P, Nelson A, Marsden SP. Org. Biomol. Chem. 2012; 10:3147. [PubMed: 22407450] Liu W-B, Xia J-B, You S-L. Top. Organomet. Chem. 2012; 38:155.
10. For examples of Ir-catalyzed intramolecular diastereoselective allylic alkylations: Wu Q-F, He H, Liu W-B, You S-L. J. Am. Chem. Soc. 2010; 132:11418. [PubMed: 20677752] Zhuo C-X, Liu W-B, Wu Q-F, You S-L. Chem. Sci. 2012; 3:205. Wu Q-F, Zheng C, You S-L. Angew. Chem., Int. Ed. 2012; 51:1680. Schafroth MA, Sarlah D, Krautwald S, Carreira EM. J. Am. Chem. Soc. 2012; 134:20276. [PubMed: 23193947] For intermolecular examples: Kanayama T, Yoshida K, Miyabe H, Takemoto Y. Angew. Chem., Int. Ed. 2003; 42:2054. Chen W, Hartwig JF. J. Am. Chem. Soc. 2013; 135:2068. [PubMed: 23286279] and ref 7.
11. Prepared in situ by treatment of $[IRcod)Cl]_2$ and phosphoramidite ligand with dry TBD Welter C, Koch O, Lipowsky G, Helmchen G. Chem. Commun. 2004:896. Shu C, Leitner A, Hartwig JF. Angew. Chem., Int. Ed. 2004; 43:4797. Hartwig JF, Stanley LM. Acc. Chem. Res. 2010; 43:1461. [PubMed: 20873839]
12. Teichert JF, Feringa BL. Angew. Chem., Int. Ed. 2010; 49:2486.
13. Zhuo C-X, Wu Q-F, Zhao Q, Xu Q-L, You S-L. J. Am. Chem. Soc. 2013; 135:8169.
14. (a) Bartels B, Helmchen G. Chem. Commun. 1999:741.(b) Bartels B, García-Yebra C, Helmchen G. Eur. J. Org. Chem. 2003:1097.(c) Polet D, Alexakis A, Tissot-Croset K, Corminboeuf C, Ditrich K. Chem. – Eur. J. 2006; 12:3596. [PubMed: 16453353] (d) Alexakis A, Polet D. Org. Lett. 2004; 6:3529. [PubMed: 15387540]
15. Absolute configuration of product **3f** determined by X-ray analysis of a derivative structure, see SI for detail. Absolute configuration of all other products determined by analogy.
16. (a) Brown HC, Okamato Y. J. Am. Chem. Soc.. 1958; 80:4979.(b) Hansch C, Leo A, Taft RW. Chem. Rev. 1991; 91:165.

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17. A similar linear relationship (ρ = −1.56±0.2, R^2 = 0.91) is observed between the log of product ratios (**3:4**) from Table 2 versus Hammett σ constants, see SI for details.
18. For mechanistic studies of the allyl-Ir complex, see ref 8b.
19. Slightly diminished dr was observed when the reaction was conducted at 50 °C, but with little change of the regioselectivity.
20. (a) Xia J-B, Liu W-B, Wang T-M, You S-L. Chem. Eur. J. 2010; 16:6442. [PubMed: 20449858] (b) Farwick A, Engelhart JU, Tverskoy O, Welter C, Umlauf QA, Rominger F, Kerr WJ, Helmchen G. Adv. Synth. Catal. 2011; 353:349.

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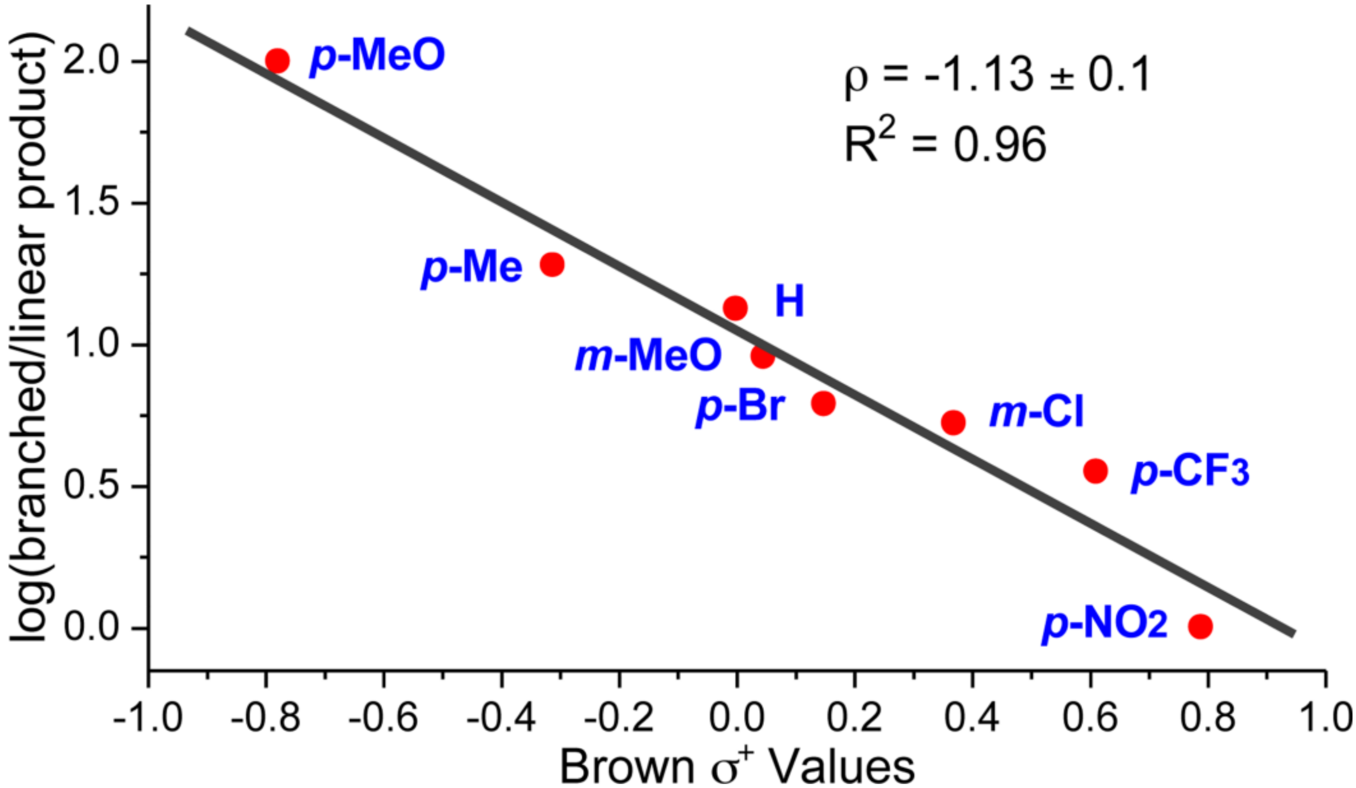
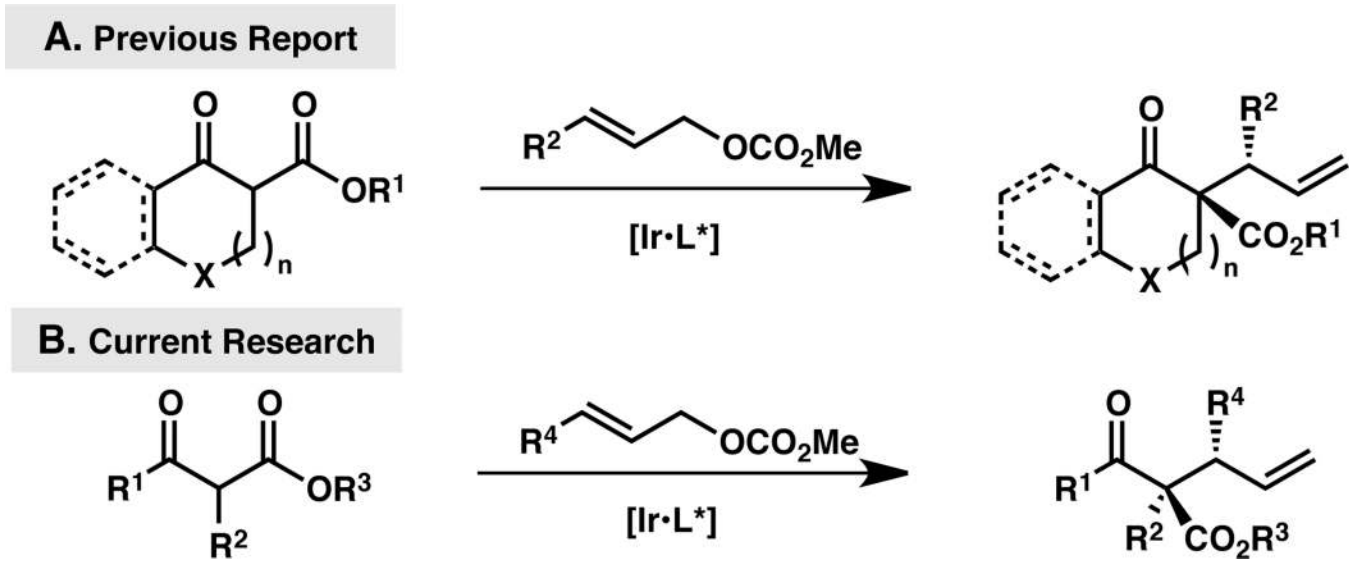
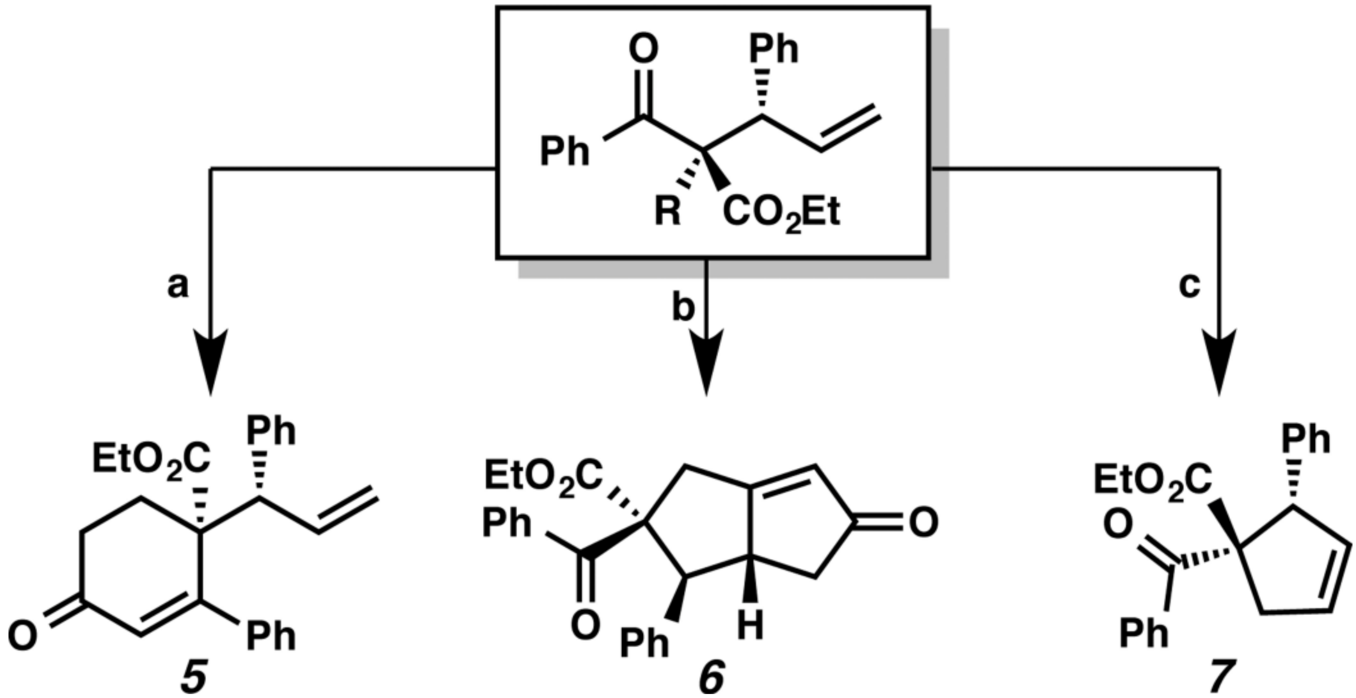


Figure 1.
Linear relationship analysis of the log of product ratios (**3:4**) from Table 2 versus Brown σ^+ values.



Scheme 1.
Representative Ir-Catalyzed Asymmetric Allylic Alkylation.



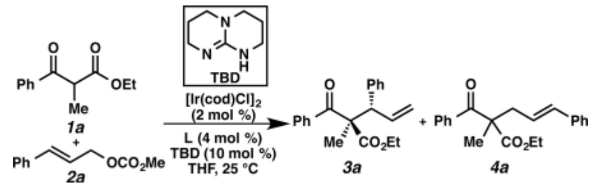
Scheme 2.

Derivatization of β-Ketoester Products.

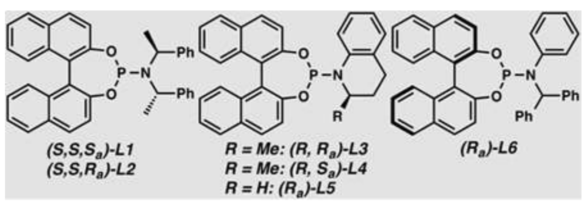
Conditions for Scheme 2: (a) **3r** (R = CH_2CH_2COMe), pyrrolidine, AcOH, *t*-BuOMe, reflux, 95% yield. (b) **3q** (R = propargyl), $Co_2(CO)_8$, CH_2Cl_2, 25 °C, then $Me_3NO \bullet 2H_2O$, >20:1 dr, 99% yield. (c) **3p** (R = allyl), Hoveyda–Grubbs II (10 mol %), CH_2Cl_2, 40 °C, 96% yield.

Table 1

Optimization of Reaction Parameters.[a]



entry	L	base/additive (x equiv)	time (h)	conv. (%)[b]	3a:4a[b]	dr of 3a[b]	ee of 3a (%)[c]
1	L1	NaH (2)	22	91	89:11	1:2	81(97)
2	L2	NaH (2)	48	46	17:83	1:1	_[d]
3	L3	NaH (2)	22	>95	95:5	13:1	99
4	L4	NaH (2)	48	34	42:58	4:1	_[d]
5	L5	NaH (2)	72	>95	71:29	2:1	76
6	L6	NaH (2)	72	>95	93:7	7:1	72
7	L3	LiBr (1)	32	>95	95:5	>20:1	>99
8	L3	LiOt-Bu (2)	2	>95	93:7	>20:1	98
9	L3	KOt-Bu (2)	4	>95	93:7	2:1	94(87)
10	L3	Cs_2CO_3 (2)	4	>95	83:17	1:2	87(94)
11	L3	DABCO (2)	24	>95	81:19	1:3	64(82)



[a]Reactions performed with 0.1 mmol of **2a**, 0.2 mmol of **1a** at 0.1 M in THF at 25 °C.

[b]Determined by ^{1}H NMR and UHPLC-MS analysis of the crude mixture.

[c]Determined by chiral SFC analysis; parenthetical value is the ee of the alternate diastereomer.

[d]Not determined.

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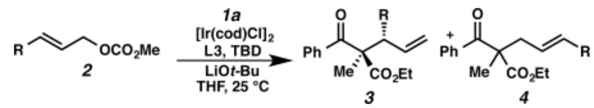
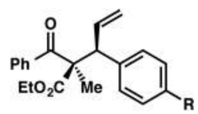
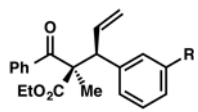
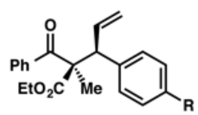
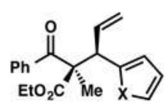
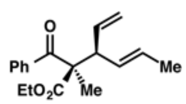
Table 2

Substrate Scope of Allyl Carbonate Electrophiles.[a]



entry	2	product (3)		yield (%)[b]	3:4[c]	dr of 3[c]	ee of 3 (%)[d]
1	*2a*		*3a* R = H	97	93:7	>20:1	98
2	*2b*		*3b* R = Me	97	95:5	20:1	>99
3[e]	*2c*		*3c* R = MeO	85	99:1	>20:1	>99
4	*2d*		*3d* R = MeO	99	90:10	17:1	>99
5	*2e*		*3e* R = Cl	98	84:16	19:1	99
6	*2f*		*3f* R = Br	98	86:14	14:1	>99
7	*2g*		*3g* R = CF_3	86	78:22	16:1	99
8	*2h*		*3h* R = NO_2	78	50:50[f]	14:1	93
9	*2i*		*3i* X = S	99	97:3	8:1	95
10	*2j*		*3j* X = O	93	95:5	13:1	>99
11	*2k*	2k 	*3k*	76	95:5	6:1	91

[a]Reactions performed under the conditions of Table 1, entry 8.

[b]Combined isolated yield of **3** and **4**.

[c]Determined by ^{1}H NMR analysis of the crude mixture.

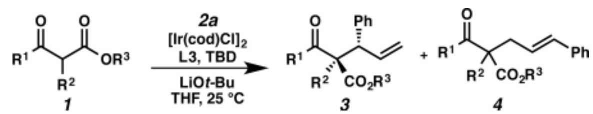
[d] Determined by chiral SFC analysis of the major diastereomer.

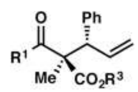
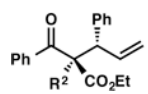
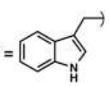
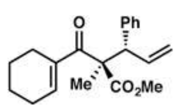
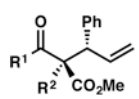
[e] Conditions of Table 1, entry 7.

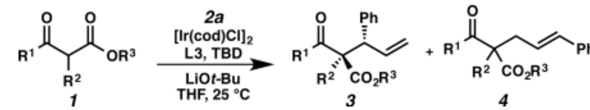
[f] 23% ee for the linear product.

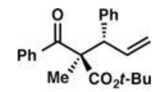
Table 3

Substrate Scope of β-Ketoesters Nucleophiles.[a]



entry	1		product (3)	yield (%)[b]	3:4[c]	dr of 3[c]	ee of 3 (%)[d]
1	1l		3l R^3 = Et R^1 = 4-MeO-C_6H_4	93	93:7	17:1	99
2	1m		3m R^3 = Me R^1 = 4-Br-C_6H_4	92	92:8	17:1	>99
3	1n		3n R^2 = Et	94	90:10	>20:1	>99
4	1o		3o R^2 = Bn	99	90:10	13:1	>99
5	1p		3p R^2 = allyl	98	95:5	>20:1	>99
6[e]	1q		3q R^2 = propargyl	84	81:19	13:1	>99
7[f]	1r		3r R^2 = $(CH_2)_2COMe$	98	93:7	20:1	99
8	1s		3s: R^2 = 	88	95:5	7:1	>99
9	1t		3t R^2 = CH_2CH_2CN	99	95:5	3:1	>99 (>99)[g]
10	1u		3u R^2 = F	92	96:4	13:1	95
11	1v		3v R^2 = Cl	96	96:4	>20:1	>99
12	1w		3w	85	90:10	12:1	99
13	1x		3x R^1 = Cy 96 R^2 = Me	92	92:8	4:1	96
14	1y		3y R^1 = Me R^2 = Et	90	93:7	1.5:1	90 (91)[g]



entry	*1*		product (*3*)	yield (%)[b]	*3:4*[c]	dr of *3*[c]	ee of *3* (%)[d]
15	*1z*		*3z*	95	70:30	6:1	>99

[a]Reactions performed under the conditions of Table 1, entry 8.

[b]Combined isolated yield of **3** and **4**.

[c]Determined by ^{1}H NMR analysis of the crude mixture.

[d]Determined by chiral SFC analysis of the major diastereomer.

[e]4 mol % of $[Ir(cod)Cl]_2$ and 8 mol % of **L3** were used.

[f]he reaction was run at 0.5 mmol scale.

[g]ee for the minor diastereomer.