Enantioselective Synthesis

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Iridium-Catalyzed Stereoselective Allylic Alkylation Reactions with Crotyl Chloride

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Dedicated to Professor Stephen F. Martin on the occasion of his 70th birthday

Abstract: *The development of the first enantio-, diastereo-, and regioselective iridium-catalyzed allylic alkylation reaction of prochiral enolates to form an all-carbon quaternary stereogenic center with an aliphatic-substituted allylic electrophile is disclosed. The reaction proceeds with good to excellent selectivity with a range of substituted tetralone-derived nucleophiles furnishing products bearing a newly formed vicinal tertiary and all-carbon quaternary stereodyad. The utility of this protocol is further demonstrated via a number of synthetically diverse product transformations.*

The synthesis of singular all-carbon quaternary stereocenters has been a long-standing challenge in the synthetic community.[1] Significant progress in this area over the past few decades has recently shifted the forefront of investigation toward the more difficult task of constructing vicinal stereodyads bearing at least one quaternary stereocenter. This nascent field is beset with difficulties not only arising from the increased sterics in the bond-forming event, but also the additional requirement of diastereocontrol. Among the available methodologies tailored for this challenge,[2,3] iridium-catalyzed allylic alkylations represent some of the most selective strategies, yet remain underdeveloped.[4]

The first iridium-catalyzed enantio-, diastereo-, and regioselective allylic alkylation was disclosed by Takemoto in 2003 and remained the sole report of such a transformation for a decade.[5] Of the ten published accounts of enantio- and diastereoselective iridium-catalyzed allylic alkylation since,[4] only five reports provide access to vicinal tertiary and *all-carbon quaternary* stereocenters.[6] However, none of these protocols tolerate the use of *aliphatic*-substituted electrophiles (Figure 1a). Conversely, the four singular examples employing aliphatic-substituted electrophiles in two published papers failed to enable construction of all-carbon quaternary stereocenters (Figure 1b).[7] While these protocols provide access to valuable chiral synthons, a wide variety of synthetic targets require the installation of aliphatic-substituted stereodyads between neighboring tertiary and quaternary carbon atoms (Figure 2). To the best of our knowledge, no transition-metal-catalyzed process allows for the creation of this desired motif. Herein, we report the first method for the iridium-catalyzed synthesis of alkyl-substituted vicinal tertiary and all-carbon quaternary stereogenic centers via allylic alkylation of prochiral enolates (Figure 1c).

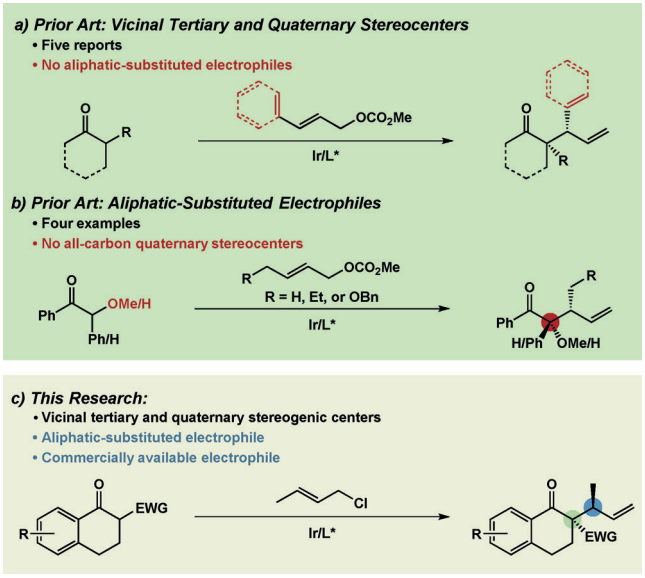

Figure 1. Enantio-, diastereo-, and regioselective iridium-catalyzed allylic alkylation reactions.

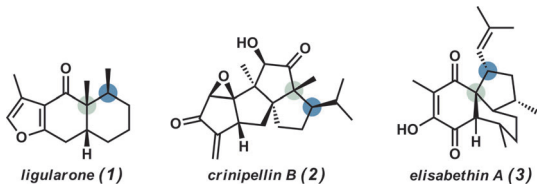

Figure 2. Select natural products bearing aliphatic-substituted vicinal tertiary and quaternary stereocenters.

Our studies commenced with an exploration of the efficacy of additives, leaving groups, bases, and ligands on the selectivity of the reaction between α-carboxymethyl tetralone (**4**) and crotyl electrophile **5**. Using our previously reported conditions for iridium-catalyzed allylic alkylations with cinnamyl-derived electrophiles as a starting point,[6a,b] the reactivity of tetralone **4** was first investigated with crotyl carbonate in the presence of catalytic phosphoramidite

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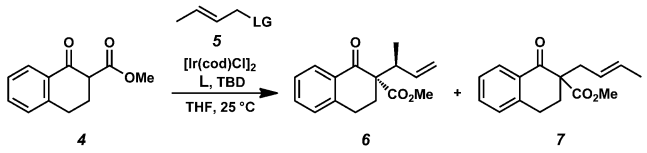
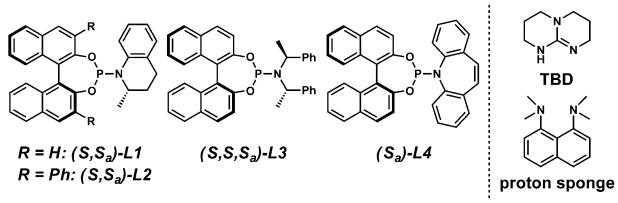
Table 1: Optimization of reaction parameters.[a]



Entry	L	Base	Additive (mol %)	LG	**4**:**5**	Yield of **6**+**7** [%][b]	**6**:**7**[c]	dr of **6**[c]	*ee* of **6** [%][d]
1	L1	–	LiBr (100)	OCO_2Me	2:1	100	55:45	6.4:1	–
2	L1	LiO*t*-Bu	–	OCO_2Me	2:1	85	34:66	5.3:1	–
3	L1	LiO*t*-Bu	LiBr (100)	OCO_2Me	2:1	100	45:55	6.8:1	–
4	L1	LiO*t*-Bu	LiCl (100)	OCO_2Me	2:1	69	50:50	7.2:1	–
5	L1	LiO*t*-Bu	LiCl (100)	Cl	2:1	94	86:14	4.8:1	–
6	L1	proton sponge	LiCl (100)	Cl	2:1	100	93:7	7.9:1	66
7	L3	proton sponge	LiCl (100)	Cl	2:1	79	69:31	2.4:1	–
8	L4	proton sponge	LiCl (100)	Cl	2:1	91	52:48	1.5:1	–
9	L2	proton sponge	LiCl (100)	Cl	2:1	46	95:5	6.0:1	96
10	L2	proton sponge	–	Cl	2:1	trace	–	–	–
11	**L2**	**proton sponge**	**LiCl (400)**	**Cl**	**2:1**	**78**	**94:6**	**6.7:1**	**97**
12	L2	proton sponge	LiCl (400)	Cl	1:1	55	95:5	5.3:1	98
13	L2	proton sponge	LiCl (400)	Cl	1:2	76	>95:5	5.3:1	85



[a] Reactions performed on 0.1 mmol scale using base (200 mol %), $[Ir(cod)Cl]_2$ (2 mol %), L (4 mol %), and TBD (10 mol %) in THF (0.1 M) at 25 °C for 18 h. [b] ^{1}H NMR yield of the mixture of diastereomers based on internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral SFC analysis. [e] TBD = 1,3,5-triazabicyclo[4.4.0]dec-5-ene, proton sponge = 1,8-bis(dimethylamino)naphthalene.

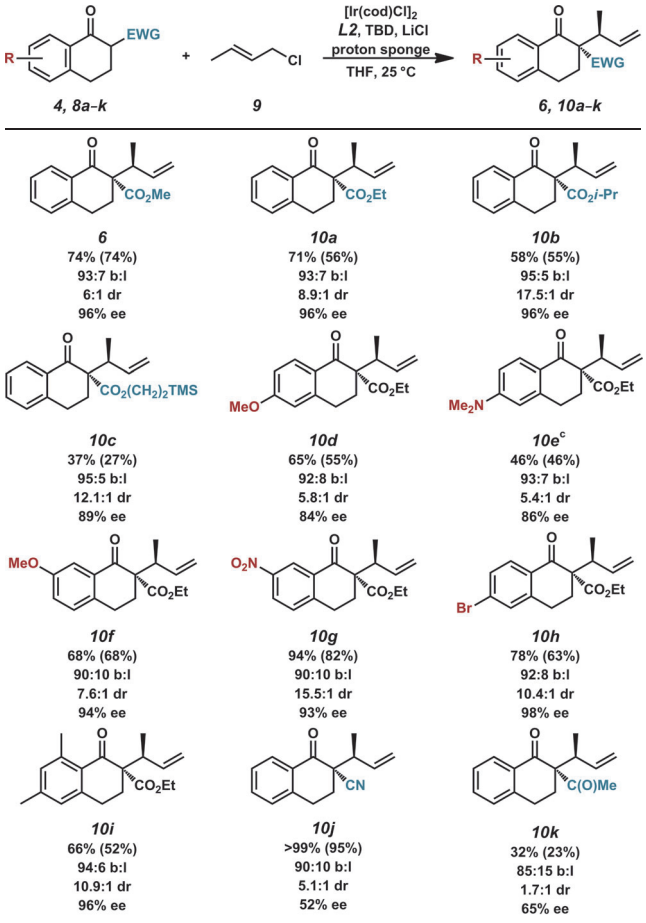
L1·$^1/_2$ $[Ir(cod)Cl]_2$ and either LiBr (Table 1, entry 1),[6a] LiO*t*-Bu (entry 2),[6b] or a combination of LiBr and LiO*t*-Bu (entry 3). Unfortunately, while these conditions resulted in excellent conversion and good diastereoselectivity, low levels of regioselectivity were observed. As our earlier work on cinnamyl-derived electrophiles revealed that the regioselectivity improved as carbocation stability increased (i.e., increasingly electron-rich aromatic cinnamyl derivatives),[6b] we reasoned that the poor regioselectivity in this case was likely due to the minimal stabilization of the carbocation afforded by the methyl substituent of **5**. Specifically, we hypothesized that the attenuated carbocation stability could be effecting slow equilibration between diastereomers of the iridium π-allyl complex, translating into diminished regioselectivity. Previous reports have proposed that LiCl may facilitate the equilibration leading to increased regio- and enantioselectivity,[10] but we noted little improvement in selectivity with the use of LiCl as compared to LiBr (entry 4).

We subsequently turned our attention to the nature of the leaving group on the electrophile. We envisioned that switching from crotyl methyl carbonate to crotyl chloride would render the anions in solution congruent and perhaps make the effect of the chloride anions more pronounced. To our delight, regioselectivity was dramatically improved with the use of crotyl chloride, albeit with diminished diastereoselectivity (entry 5).

Previous work demonstrating the marked effect of bases on regio- and diastereoselectivity in iridium-catalyzed allylic alkylations prompted an extensive exploration of bases (see Supporting Information for details).[5–8] We found that the use of proton sponge in place of LiO*t*-Bu afforded the desired branched product **6** with high regioselectivity (93:7, **6**:**7**) and diastereoselectivity (7.9:1 dr), though in a modest 66 % enantiomeric excess (entry 6). A brief study of ligand frameworks (entries 7–9)[9] revealed 3,3′-diphenyl-phosphoramidite **L2** to be optimal. Using **L2**, allylic alkylation product **6** was obtained in excellent enantioselectivity (96 % *ee*) with comparable regio- and diastereoselectivities to **L1**, though in considerably lower yield (entry 9). Efforts to increase the yield revealed super-stoichiometric levels of LiCl to be both essential and correlative to the conversion (entries 10 and 11). Ultimately, we found that the combination of catalytic phosphoramidite **L2**·$^1/_2$ $[Ir(cod)Cl]_2$, 200 mol % proton sponge, and 400 mol % LiCl delivered product **6** in 78 % yield (entry 11) with an exceptional branched to linear ratio (94:6, **6**:**7**), diastereoselectivity (6.7:1 dr), and enantioselectivity (97 % *ee*). Finally, it should be noted that we observed optimal conversion and selectivity using a 2:1 nucleophile to electrophile ratio; however, the nucleophile and electrophile stoichiometry could be varied (1:1 or 1:2) without dramatically affecting reaction conversion or selectivity, rendering the reaction synthetically practical (entries 12 and 13).[10]

With the optimized conditions identified, we explored the substrate scope of this enantio-, diastereo-, and regioselective allylic alkylation reaction (Table 2). Generally, the process is tolerant of a wide range of substituents and functionality on both the arene and ester groups.[12] We found that increasing the size of the ester moiety ($-CO_2Me$, $-CO_2Et$, $-CO_2i$-Pr) resulted in formation of the corresponding products **6**, **10a**, and **10b** in increasingly improved regio- and diastereoselectivity but moderately diminished yields. As a balance between yield and selectivity, we moved forward in our investigation using α-carboxyethyl tetralone derivatives. Moreover, we were pleased to find that a (2-trimethylsilyl)ethyl substrate underwent allylic alkylation to provide **10c** with good

Table 2: Substrate scope exploration.[a,b]



[a] Reactions performed with **9** (0.2 mmol), **4** or **8** (200 mol %), proton sponge (200 mol %), $[Ir(cod)Cl]_2$ (2 mol %), **L2** (4 mol %), and TBD (10 mol %) in THF (0.1 M) at 25 °C for 18 h. [b] ^{1}H NMR yield of the mixture of diastereomers based on internal standard; combined isolated yield of branched and linear products given in parentheses; regioselectivity of the crude reaction mixture; *ee*'s determined by chiral SFC or HPLC analysis. [c] Absolute stereochemistry determined via single-crystal X-ray analysis.

selectivity, albeit in modest yield. Alkylation product **10c** may undergo subsequent fluoride-triggered allylic alkylation mediated by palladium to provide either diastereomer of the bis-alkylation product with catalyst control.[13]

We sought to further examine the scope of the reaction by exploring the diversity of substitution permitted on the tetralone aromatic ring. Gratifyingly, a wide variety of both electron-donating and withdrawing groups were tolerated at varying positions, though an electronic effect was noted on enantioselectivity. We observed that substrates bearing electron-donating groups (MeO–, Me_2N–) at the 6-position gave products **10d** and **10e** with slightly diminished enantioselectivity (84–86% *ee*). Conversely, substrates with electron-withdrawing groups (7-MeO–, 7-NO_2–, 6-Br–) afforded the corresponding products **10f**, **10g**, and **10h** in excellent enantioselectivity (94–98% *ee*). Additionally, 5,7-dimethyl-substituted tetralone **10i** was furnished in comparable selectivity to unsubstituted α-carboxyethyl tetralone **10a**. In all examples, good regio- and diastereoselectivity was observed.

Furthermore, during the course of our investigations we found that the β-keto ester moiety was crucial to the reaction. Substrates with this functionality replaced with either a nitrile or ketone provided the corresponding products **10j** and **10k** in decreased selectivities. No allylic alkylation was observed with aliphatic-substituted allyl chloride derivatives other than of crotyl chloride.

To demonstrate the synthetic utility of this method, we carried out a number of transformations on allylic alkylation products **6** and **10a** (Figure 3). We found that the addition of allylmagnesium chloride proceeded smoothly to furnish alcohol **11** in 71% yield. In a two-step protocol, addition of

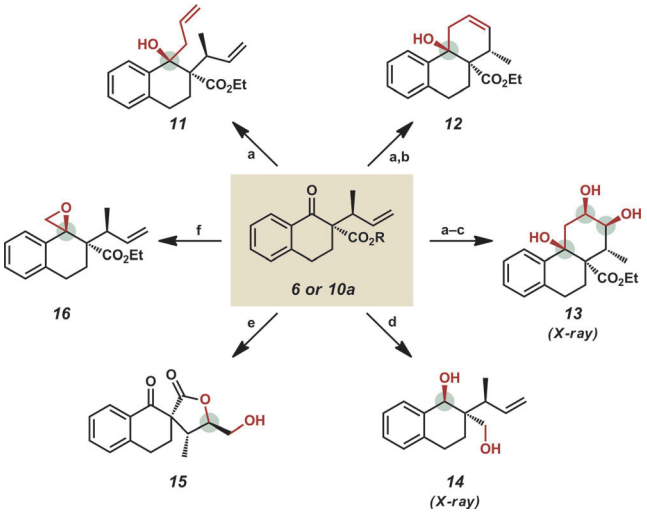


Figure 3. a) Allylmagnesium chloride, THF, −78 °C, 71%. b) HG-II, CH_2Cl_2, 81%. c) K_2OsO_4, NMO, THF/H_2O, 59%. d) DIBAL, THF, −78 °C, 43%. e) K_2OsO_4, NMO, THF/H_2O, 65%. f) $Me_3S(O)I$, NaH, DMSO, 82%.

allyl Grignard with subsequent ring-closing metathesis allowed rapid access to tricycle **12** bearing three contiguous stereocenters in 58% yield over two steps. The resultant cyclohexene moiety underwent dihydroxylation to provide triol **13** bearing five contiguous stereogenic centers in 59% yield. Both the ester and the ketone functionalities of **10a** were reduced to provide 1,3-diol **14** in 43% yield. Dihydroxylation of the pendant olefin of **10a** proceeded with concomitant lactonization to provide highly functionalized γ-butyrolactone **15** in 65% yield. Functionalized γ-butyrolactone moeites are highly prevalent and estimated to be present in about 10% of all natural products.[14] Additionally, Corey-Chaykovsky epoxidation proceeded smoothly, furnishing **16** in 82% yield. Notably, all six of these derivatizations proceed with excellent diastereoselectivity to facilitate the synthesis of at least three contiguous stereogenic centers, demonstrating the ease with which complexity can be added to these high-value products.

In summary, we have developed the first enantioselective transition-metal-catalyzed allylic alkylation reaction forming vicinal tertiary and all-carbon quaternary stereocenters between prochiral enolates and an aliphatic-substituted electrophile. Critical to the success of this new reaction is

the identity and ubiquity of the chloride counterion in addition to the use of proton sponge, the combination of which affords excellent regio- and enantioselectivities along with good yields and diastereoselectivities. Additionally, a number of transformations were carried out on the alkylation products to demonstrate the value of this method in rapidly accessing highly functionalized, stereochemically rich polycyclic scaffolds. Further explorations to expand this chemistry to include additional aliphatic-substituted electrophiles and to broaden the nuclophile scope are currently underway and will be reported in due course.

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Keywords: allylic alkylation · enantioselective synthesis · iridium · quaternary stereocenter · vicinal stereocenters

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[12] The use of indanone or benzosuberone nucleophiles led to significantly decreased diastereoselectivities, as did heteroatom substitution within the aromatic and aliphatic rings (e.g. 2,3-dihydro-4*H*-1-benzopyran-4-one).

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Communications

Enantioselective Synthesis

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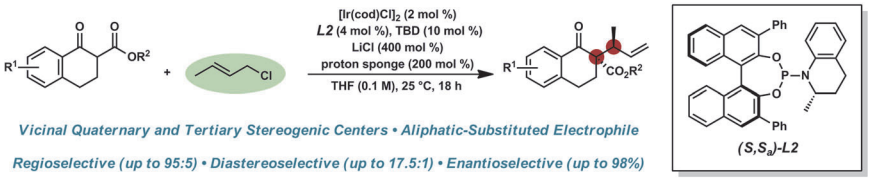
Iridium-Catalyzed Stereoselective Allylic Alkylation Reactions with Crotyl Chloride



Sponge worthy: The unique combination of crotyl chloride, LiCl, and proton sponge has delivered the first enantio-, diastereo-, and regioselective iridium-catalyzed allylic alkylation reaction to form an all-carbon quaternary stereocenter with an aliphatic-substituted electrophile. The reaction proceeds with good to excellent selectivity for a range of substituted tetralones providing products bearing a newly formed vicinal tertiary and all-carbon quaternary stereodyad.