Organic LETTERS

Letter

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Development of (Trimethylsilyl)ethyl Ester Protected Enolates and Applications in Palladium-Catalyzed Enantioselective Allylic Alkylation: Intermolecular Cross-Coupling of Functionalized Electrophiles

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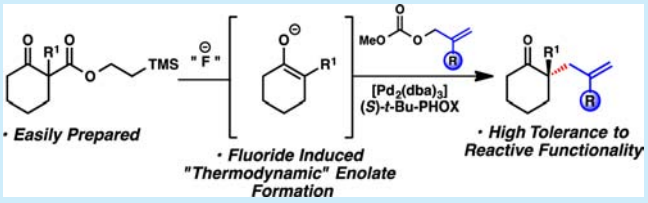
Supporting Information

ABSTRACT: The development of (trimethylsilyl)ethyl ester protected enolates is reported. The application of this class of compounds in palladium-catalyzed asymmetric allylic alkylation is explored, yielding a variety of α-quaternary six- and seven-membered ketones and lactams. Independent coupling partner synthesis engenders enhanced allyl substrate scope relative to traditional β-ketoester substrates; highly functionalized α-quaternary ketones generated by the union of (trimethylsilyl)ethyl β-ketoesters and sensitive allylic alkylation coupling partners serve to demonstrate the utility of this method for complex fragment coupling.



Latent or protected enolates such as silyl enol ethers, silyl ketene acetals, allyl enol carbonates, allyl β-keto esters, and others have found broad use in organic synthesis owing to their mild release and ease of use.[1] Perhaps the most well studied class of protected enolates employ oxygen-bound protecting groups (i.e., silyl enol ethers). Unfortunately, the utility of this class of compounds is often limited by poor regioselectivity when forming fully substituted enol derivatives.[2] Although much effort has been devoted to the identification of conditions that allow for selective generation of so-called "thermodynamic" enolate isomers, selectivity often drops precipitously when sterically demanding α-substitution is introduced.[3] This problem would be solved, ideally, by the development of enolate precursors that are readily prepared and, when triggered, release the "thermodynamic" enolate under kinetic control.

In the context of allylic alkylation reactions, carboxylate-protected enolates (i.e., allyl β-ketoesters, e.g., **I**, Figure 1A) represent a significant advance toward such a solution. Allyl β-ketoesters enjoy relatively uncomplicated, selective synthesis[4] and mild deprotection, resulting in enolate formation following decarboxylation.[5] Despite these advantages, facile nucleophilic attack of the incipient enolate at the transition metal-allyl species generated during deprotection often precludes applications that do not involve allylic alkylation.[6] Moreover, with traditional carboxylate-protected enolates any functionality borne by the allyl fragment (R^2, Figure 1A) must be compatible with the conditions required for substrate synthesis (i.e., strong base and reactive electrophiles, Figure 1A). Tunge and co-workers have demonstrated the utility of acyl-protected

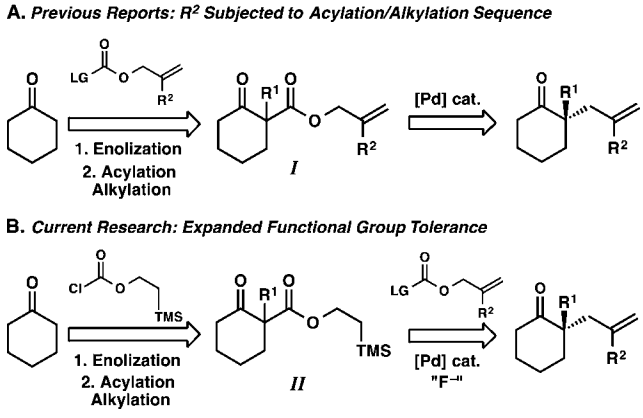


Figure 1. New substrate design enables broader functional group (R^2) scope in allylic alkylation reactions.

enolates, which may undergo deprotection via a retro Claisen condensation to reveal fully substituted enolates that participate in catalysis.[7] However, these reactions often require the use of elevated temperatures and alkoxide base to proceed.

In a recent communication,[8] we disclosed a novel class of substrates for enolate alkylation chemistry,[9] (trimethylsilyl)-ethyl β-ketoesters (TMSE β-ketoester), that undergo mild deprotection upon treatment with a fluoride source, and we demonstrated their use in the diastereoselective allylic alkylation of cyclic β-ketoesters. The TMSE β-ketoester

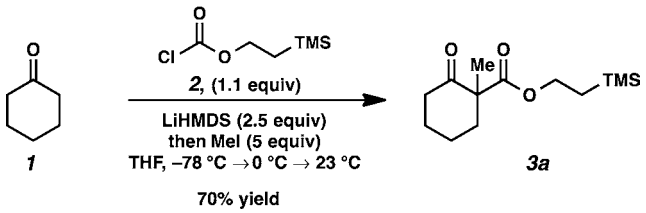
Received: February 3, 2014
Published: April 11, 2014

   dx.doi.org/10.1021/ol500355z | Org. Lett. 2014, 16, 2314−2317

substrate class (i.e., **II**, Figure 1B) boasts similar ease of preparation as compared with allyl β-ketoesters but is not susceptible to transition metal-mediated deprotection, a benefit that enabled sequential transition metal-catalyzed allylic alkylation events in our previous work.[8] We hypothesized that use of TMSE β-ketoesters may enhance the breadth of functional group tolerance at the allyl coupling partner in asymmetric allylic alkylations, relative to allyl β-ketoesters, by virtue of the fact that the allyl fragment is not subjected to the conditions of substrate synthesis (Figure 1B). In this report, we describe the preparation and development of this substrate class and the evaluation thereof in the enantioselective palladium-catalyzed allylic alkylation of six- and seven-membered ketone and lactam scaffolds. Furthermore, we go on to show how the use of these substrates can enable the union of complex fragments bearing functionality that would be incompatible with incorporation into traditional allyl β-ketoester substrates.

In considering novel carboxylate protected enolates, our design criteria called for a substrate that could be synthesized efficiently and deprotected under mild conditions and facilitate the convergent union of complex fragments in a synthetic setting. To address these concerns we chose to explore 2-(trimethylsilyl)ethyl 1-alkyl-2-oxocyclohexane-1-carboxylates or TMSE β-ketoesters. We were pleased to find that α-methyl TMSE β-ketoester (**3a**) could be prepared in a single synthetic operation from commercially available cyclohexanone (**1**), 2-(trimethylsilyl)ethyl chloroformate (**2**), and methyl iodide (MeI) in good overall yield (Scheme 1).

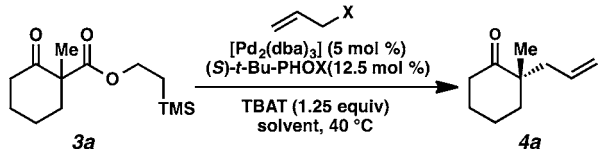
Scheme 1. Synthesis of TMSE β-Ketoester



With TMSE β-ketoester **3a** in hand, our investigation into this substrate class commenced in the context of palladium-catalyzed allylic alkylation. We were pleased to find that exposure of β-ketoester **3a** to allyl bromide, tetrabutylammonium difluorotriphenylsilicate (TBAT), $[Pd_2(dba)_3]$, and (*S*)-*t*-Bu-PHOX[10] in toluene at 40 °C generated the desired α-quaternary ketone **4a** in modest yield and good enantioselectivity (entry 1, Table 1). We next explored the scope of allyl sources that could be used in the reaction and found that a variety of diverse allyl sources were competent in the chemistry, including allyl sulfonates, allyl acetates, and allyl carbonates (entries 2–5). Allyl methyl carbonate proved to be the most efficient, selective, and prudent allyl source, in particular with respect to the number of the allyl equivalents required for optimal reactivity (entry 6). Reaction parameters including relative stoichiometry (entries 7–9), solvent (entries 10–13), and temperature (entry 14) were all subsequently explored and, ultimately, we found that a slight excess of mixed carbonate in THF at 25 °C proved optimal, delivering the desired ketone in 81% yield and 86% enantioselectivity (entry 14).

Having identified optimal reaction conditions, we turned our attention to exploring reaction scope, beginning with tolerance of variability with respect to the nucleophile's α-substitution, ring size, and carbonyl functionality (Figure 2). Simple α-alkyl

Table 1. Optimization of Reaction Parameters[11]



entry	X	equiv allyl	sovent	yield (%)[a]	ee (%)[b]
1	Br	1.0	toluene	55	83
2	OTs	1.0	1,4-dioxane	43	77
3	OMs	1.0	1,4-dioxane	45	84
4	OAc	1.0	1,4-dioxane	15	82
5	OCO_2Allyl	1.0	1,4-dioxane	78	83
6	OCO_2Me	1.0	1,4-dioxane	78	84
7	OCO_2Me	0.75	1,4-dioxane	51	82
8	OCO_2Me	1.5	1,4-dioxane	74	82
9	OCO_2Me	2.0	1,4-dioxane	73	84
10	OCO_2Me	1.1	toluene	33	82
11	OCO_2Me	1.1	MTBE	65	84
12	OCO_2Me	1.1	THF	83	83
13	OCO_2Me	1.1	tol/hex	45	93
14[c]	OCO_2Me	1.1	THF	81	86

[a]Yield determined by comparison to tridecane internal standard. [b]Percent ee determined by chiral GC analysis of the crude reaction mixture. [c]Reaction performed at 25 °C.

substitutions, such as α-benzyl substituted β-ketoester **3b** (R^1 = Bn, X = Y = CH_2, n = 1, Figure 2), functioned consistently well in the chemistry; the desired benzyl substituted α-quaternary ketone **4b** was obtained in high yield and enantioselectivity. In addition to simple α-alkyl substrates (i.e., compounds **3a** and **3b**), heteroatom-substituted substrate **3c** (R^1 = F, X = Y = CH_2, n = 1) proved to be a viable coupling partner and provided the corresponding α-fluoro-allylic alkylation product **4c** in good yield and excellent ee. Subjecting methyl ester bearing substrate **3d** (R^1 = $CH_2CH_2CO_2Me$, X = Y = CH_2, n = 1) to our optimized conditions resulted in an efficient and selective reaction, furnishing enantioenriched ketone **4d** in 93% yield and 89% ee. Substrates constituted from seven-membered rings, including ketone **3e** (R^1 = Me, X = Y = CH_2, n = 2) and vinylogous ester **3f** (R^1 = Me, X = CH, Y = CO(*i*-Bu), n = 2), were shown to be suitable coupling partners, affording α-quaternary ketone **4e** and α-quaternary vinylogous ester **4f** products in 95% and 89% yield and 87% and 92% ee, respectively. Finally, six- and seven-membered lactams were investigated. We were pleased to find that under slightly modified reaction conditions (40 °C), the desired α-functionalized lactam products **4g** and **4h** were obtained in good to excellent yields and excellent ee's.

Having surveyed the scope of reaction with respect to nucleophile α-substitution and scaffold type, we next probed the reaction with respect to substitution at the 2-allyl position. We were pleased to find that a variety of functional groups could be introduced through the use of variously substituted allyl carbonates (**5**, $R^2 \neq$ H, Figure 2). Simple alkyl substitution at the internal allyl position was well tolerated as 2-methylallyl ketone **4i** was obtained in 89% yield and 89% ee. 2-Chloroallyl

dx.doi.org/10.1021/ol500355z | *Org. Lett.* 2014, 16, 2314–2317

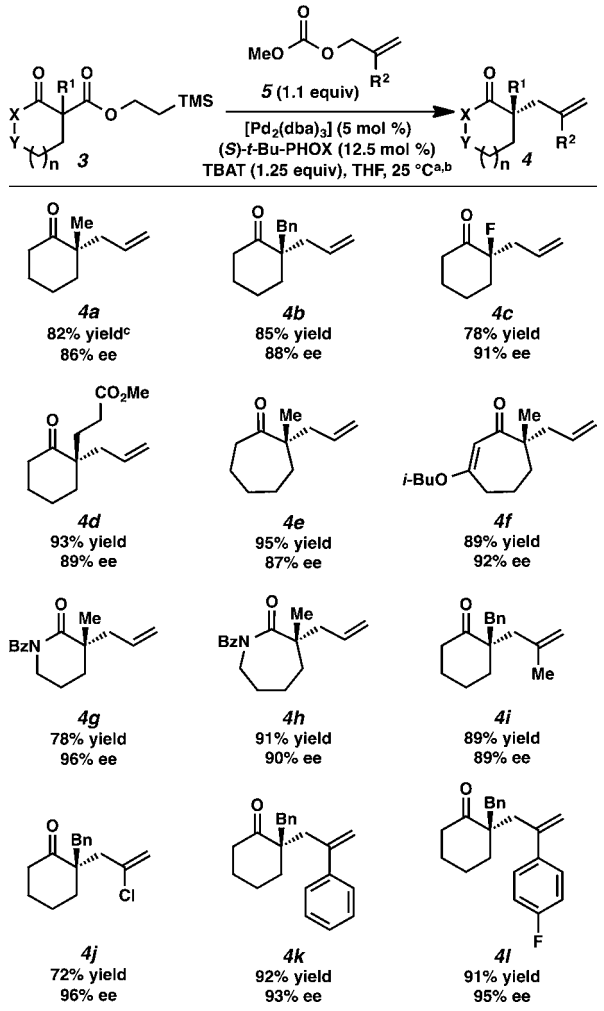


Figure 2. Exploration of functional group and scaffold diversity in the fluoride-triggered palladium-catalyzed allylic alkylation reaction. Notes: (a) Reaction conditions: **3** (1.0 equiv), **5** (1.1 equiv), $[Pd_2(dba)_3]$ (5 mol %), (*S*)-*t*-Bu-PHOX (12.5 mol %), and TBAT (1.25 equiv) in THF (0.033 M) at 25 °C for 12−48 h. (b) Reaction performed on substrates **3k** and **3l** at 40 °C. (c) All reported yields are for isolated products.

methyl carbonate (**5**, R^2 = Cl) also participated well in the chemistry, furnishing the corresponding α-quaternary ketone **4j** in 72% yield and 96% ee. Allyl fragments bearing electron-neutral and electron-deficient aryl groups also functioned well in the reaction, delivering the desired products **4k** and **4l**, respectively, in excellent yields and ee's.

While the new fluoride-triggered chemistry described thus far permits alternative access to structures previously available by allylic alkylation, a distinct advantage offered by TMSE β-ketoesters in allylic alkylation chemistry is the ability to introduce allyl-coupling partners that would be unstable to the conditions of allyl β-ketoester substrate synthesis. To illustrate this feature of the new chemistry, we synthesized mixed carbonates **6** and **7** as coupling partners for palladium-catalyzed allylic alkylation (Figure 3). Allyl carbonate **6**, derived from leucine, bears an epimerizable stereocenter that is racemized upon treatment with strong base.[12] Because strong base (i.e., LDA, LHMDS, etc.) is typically required for enolization and acylation in the preparation of standard allyl β-ketoesters, employing electrophiles bearing base-labile functionality has not been previously possible. Alternatively, allyl carbonate **7**,

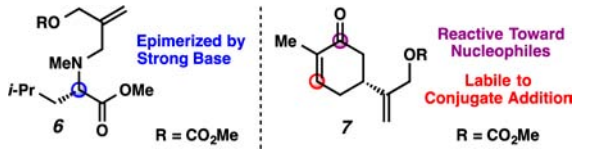
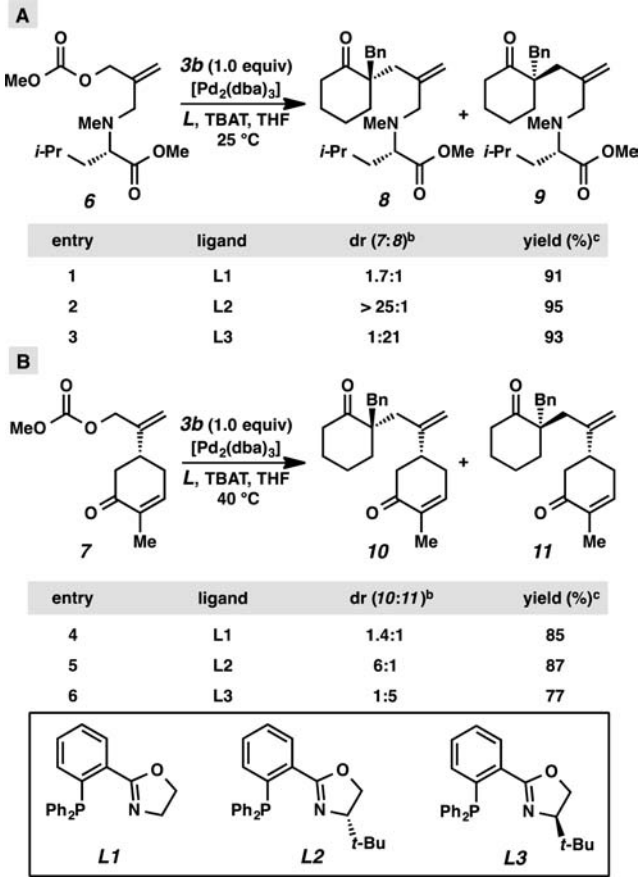


Figure 3. Complex allyl architectures.

which was synthesized by allylic oxidation of (*S*)-carvone, also bears functionality that would be unstable to the conditions required for standard allyl β-ketoester substrate synthesis. In particular, we envisioned that attempts to acylate a ketone enolate with an allyl chloro- or allyl cyanoformate bearing enone **7** would be complicated by undesired conjugate addition and enolate chemistries (e.g., aldol reaction, Michael addition, etc.). In both cases, our new TMSE β-ketoester chemistry allows for the independent preparation and, thus, physical separation of nucleophilic and electrophilic components until the enantioselective fragment coupling stage.

Subjecting allyl carbonate **6** and TMSE β-ketoester **3b** (R^1 = Bn, X = Y = CH_2, n = 1, Figure 2) to our fluoride-modified allylic alkylation conditions with achiral ligand **L1** revealed modest substrate-controlled diastereoselection of 1.7:1 (entry 1, Table 2A). Use of (*S*)-*t*-Bu-PHOX (**L2**) resulted in a highly

Table 2. Union of Complex Fragments by Asymmetric Allylic Alkylation[a]



entry	ligand	dr (7:8)[b]	yield (%)[c]
1	L1	1.7:1	91
2	L2	> 25:1	95
3	L3	1:21	93

entry	ligand	dr (10:11)[b]	yield (%)[c]
4	L1	1.4:1	85
5	L2	6:1	87
6	L3	1:5	77

[a]Reaction conditions: **3b** (1.0 equiv), **6** or **9** (1.1 equiv), $[Pd_2(dba)_3]$ (5 mol %), ligand (12.5 mol %), and TBAT (1.25 equiv) in THF (0.033 M) at the indicated temperature for 24−48 h. [b]Diastereoselectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Yields are reported for the combined diastereomeric mixture.

dx.doi.org/10.1021/ol500355z | Org. Lett. 2014, 16, 2314−2317

efficient and diastereoselective reaction giving the desired amino ester **8** in 95% yield and greater than 25:1 dr, with no detectable epimerization at the amino ester side chain (entry 2). The inherent diastereoselectivity could be completely reversed under catalyst control by using (*R*)-*t*-Bu-PHOX (**L3**), without significant loss in selectivity or reactivity (entry 3). Likewise, upon exposing carbonate **7** and ketoester **3b** to slightly modified allylic alkylation conditions (40 °C) with an achiral ligand, we again observed an efficient reaction and slight inherent diastereoselectivity (entry 4, Table 2B). This bias could be enhanced by using ligand **L2** to obtain α-quaternary ketone **10** in 6:1 dr and 87% yield or overturned by use of **L3** to obtain **11** in 5:1 dr and 77% yield (entries 5 and 6).

In conclusion, we have developed a new class of substrates for enolate alkylation chemistry that benefit from ease of preparation and mild deprotection conditions that are orthogonal to those used with traditional allyl β-ketoesters. We examined the application of these compounds in palladium-catalyzed asymmetric allylic alkylation chemistry and found that a wide range of functional groups and substrate scaffolds are well tolerated, including six- and seven-membered ketones and lactams. We have further demonstrated the value of these compounds for uniting complex coupling partners that would be incompatible to preparation via standard allyl β-ketoester based allylic alkylation. We envision this technology will also enable the convergent cross-coupling of synthetically challenging fragments for complex molecule synthesis. Further studies exploring the application of TMSE β-ketoesters in diverse reaction methodologies and complex natural product synthesis are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, the Caltech Center for Catalysis and Chemical Synthesis, and Caltech for financial support. C.M.R. thanks the Rose Hills Foundation for a predoctoral fellowship. The authors thank Scott Virgil (Caltech) for helpful discussions and instrumentation assistance. Rob Craig (Caltech) and Dr. Allen Hong (Caltech) are thanked for helpful discussion.

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