

Enantioselective Pd-Catalyzed Decarboxylative Allylic Alkylation of Thiopyranones. Access to Acyclic, Stereogenic α -Quaternary Ketones

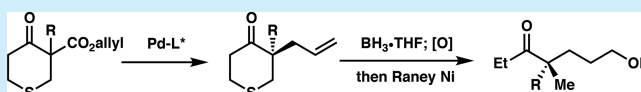
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S Supporting Information

ABSTRACT: A catalytic, enantioselective decarboxylative allylic alkylation of 4-thiopyranones is reported. The α -quaternary 4-thiopyranones produced are challenging to access by standard enolate alkylation owing to facile ring-opening β -sulfur elimination. In addition, reduction of the carbon–sulfur bonds provides access to elusive acyclic α -quaternary ketones. The alkylated products are obtained in up to 92% yield and 94% enantiomeric excess.



The enantioselective construction of all-carbon quaternary stereogenic centers, particularly acyclic ones, is a significant challenge in organic synthesis.¹ Among the most reliable methods available for forming all-carbon quaternary stereocenters, such as conjugate addition and sigmatropic rearrangements, palladium-catalyzed decarboxylative allylic alkylation has become a widely adopted and studied transformation owing to its mild nature, broad scope, and versatility of the introduced allyl group for further synthetic manipulations.² The mild nature of this transformation was hypothesized to allow access to α -quaternary 4-thiopyranones, which are troublesome to access through standard enolate chemistry owing to the β -disposed sulfur and the propensity for forming ring-opened sulfur alkylation products.³ Despite these disadvantages, such heterocyclic ketones have been shown to undergo aldol⁴ and Mannich⁵ reactions, although degradation of the products by retro-aldol processes during purification is common.⁶ The thiopyranone motif has also been shown to tolerate amine, thiourea dual catalysis for enantioselective conjugate addition to form an α -quaternary 4-thiopyranone in an enantioenriched fashion.⁷ The value of this motif has been demonstrated by its use as a building block in medicinal chemistry applications;⁸ therefore, new methods for constructing chiral, enantioenriched thiopyranone derivatives would allow access to new chemical space.

Our approach would entail a palladium-catalyzed decarboxylative allylic alkylation of a thiopyranone allyl β -ketoester (**1a**, Table 1), which would allow access to a diverse range of α -quaternary 4-thiopyranones in an enantioselective fashion. Indeed, a general strategy that has been reported to access alkylated 4-thiopyranones is by first α -functionalization of the corresponding β -ketoester followed by decarboxylation⁹ or tin hydride mediated addition of alkyl and aryl halides.¹⁰

In addition to accessing a synthetically challenging quaternary stereocenter, we also envisioned utilizing the sulfur as a removable handle to access acyclic, all-carbon quaternary

Table 1. Optimization of Alkylation Conditions^a

entry	Pd source	ligand	solvent	yield ^b	ee ^{c,d}
1	Pd(dba) ₂	(S)-L1	THF	NR	
2	Pd(dba) ₂	(S)-L2	THF	24	–78
3	Pd(dba) ₂	(R,R)-L3	THF	<5	24
4	Pd(dba) ₂	(R,R)-L4	THF	<5	66
5	Pd(dba) ₂	(R,R)-L5	THF	85	69
6	Pd(dba) ₂	(R,R)-L5	dioxane	<i>e</i>	54
7	Pd(dba) ₂	(R,R)-L5	EtOAc	<i>e</i>	73
8	Pd(dba) ₂	(R,R)-L5	toluene	<i>e</i>	83
9	Pd(dba) ₂	(R,R)-L5	benzene	<i>e</i>	78
10	Pd(dba) ₂	(R,R)-L5	hexane/toluene (2:1)	<i>e</i>	80
11	Pd(dba) ₂	(R,R)-L5	TBME	78	87
12	[PdCl(allyl)] ₂	(R,R)-L5	TBME	<i>e</i>	90
13	Pd(dmdba) ₂	(R,R)-L5	TBME	<i>e</i>	91
14	Pd ₂ (pmdba) ₃	(R,R)-L5	TBME	90	93
15 ^f	Pd ₂ (pmdba) ₃	(R,R)-L5	TBME	92	94

^aConditions: 0.1 mmol of **1a**, 2.5 mol % of Pd₂(dba)₃, 6 mol % of ligand, 1 mL of solvent. ^bYield of isolated product. ^cDetermined by chiral SFC. ^dAbsolute configuration determined by vibrational circular dichroism. ^eConversion not monitored. ^fReaction performed with 0.2 mmol of **1a**, 1.0 mol % of Pd₂(pmdba)₃, 2.4 mol % of ligand, and 2 mL of solvent.

stereocenters^{1c} by treatment with Raney nickel. Exploiting a rigid, cyclic thioether to access stereodefined acyclic systems is a valuable strategy utilized in organic synthesis to access

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polypropionates, most notably Woodward's synthesis of erythromycin,¹¹ with this chemistry later expanded upon by other research groups.¹² By using a cyclic system, the issue of controlling tri- and tetrasubstituted enolate geometry, a difficult task in acyclic molecules, is circumvented. While certain acyclic trisubstituted enolates can be formed with a high degree of stereochemical fidelity (e.g., oxizolidinones), the methodology to produce tetrasubstituted enolates en route to all-carbon quaternary stereocenters is less developed. A notable example comes from the Marek laboratory, in which a stereoselective carbometalation of alkynes is exploited en route to a number of different motifs including homoallylic alcohols¹³ and aldol adducts.¹⁴ In fact, only a few reports of forming enantioenriched acyclic α -quaternary ketones exist in the literature.¹⁵

We initiated our investigations with α -benzyl β -ketoester **1a** and phosphinoxazoline (PHOX) ligands **L1** and the electronically deficient **L2**, used previously by our group for asymmetric allylic alkylation (Figure 1 and Table 1).^{2a} Initial reactions

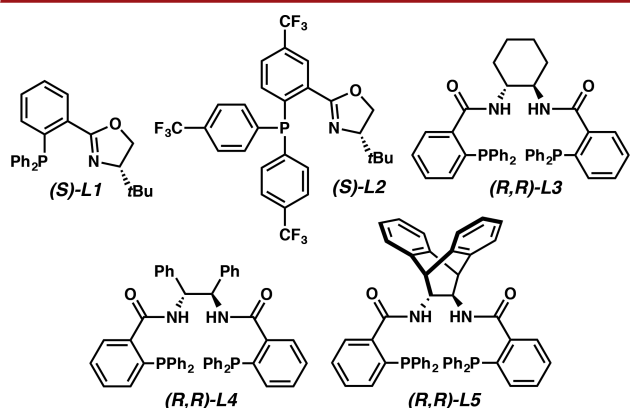


Figure 1. Representative ligands examined.

employed 5 mol % of $\text{Pd}(\text{dba})_2$ and 6 mol % of ligand in THF. The presence of the Lewis basic sulfur was envisioned to be trivial owing to prior examples of such functionalities (i.e., thioethers) being tolerated under analogous conditions.^{2a} Unfortunately, in this case, both PHOX ligands performed poorly, producing either no reaction with **L1** (entry 1) or low conversion with **L2** (entry 2), albeit in moderate enantiomeric excess.

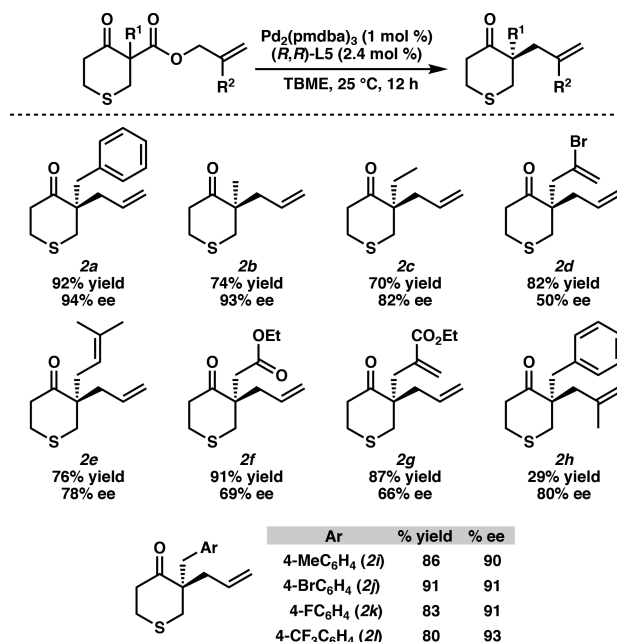
Bisphosphine ligands **L3** and **L4**^{2b} were found to perform equally poorly, providing very low conversion to product (>5%) and enantiomeric excesses of 24 and 66%, respectively (entries 3 and 4). On the other hand, anthracene diamine derived bisphosphine **L5** was found to affect the desired transformation in 85% isolated yield and 69% enantiomeric excess (entry 5). Despite obtaining a lower enantiomeric excess with **L5** compared to **L2**, the improved reactivity was promising, and further optimization efforts focused on **L5** (36 additional ligands were examined; see the SI for details).

With the ideal ligand identified, the remaining reaction parameters were examined. More polar solvents such as dioxane and EtOAc were found to give decreased enantiomeric excesses of 54% and 73%, respectively (entries 6 and 7). The use of toluene resulted in an increased enantiomeric excess of 83% (entry 8), while benzene and a 2:1 mixture of hexane/toluene were found to give slightly lower levels of selectivity (entries 9 and 10). TBME provided an elevated enantiomeric excess of 87% (entry 11) and was advanced further as the solvent of

choice. Additional improvements in enantioselectivity were achieved with different palladium sources (entries 12–14), with $\text{Pd}_2(\text{pmdba})_3$ providing the best result and furnishing the α -quaternary thiopyranone in 90% isolated yield and 93% enantiomeric excess (entry 14). Lastly, it was found that lowering the loading of catalyst and ligand by 2.5 times resulted in no loss of either yield or enantiomeric excess, with only a modest increase in reaction time from 3 to 9 h (entry 15); therefore, this lowered loading was used for the remainder of the experiments. The absolute stereochemistry of **2a** was determined via vibrational circular dichroism (see the SI for details).

With the optimized conditions identified, a variety of different α -substituents were examined in order to evaluate the scope of the chemistry (Scheme 1).¹⁶ Simple alkyl groups,¹⁷

Scheme 1. Substrate Scope^a

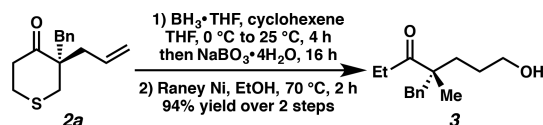


^aConditions: 0.2 mmol of β -ketoester, 1.0 mol % of $\text{Pd}_2(\text{pmdba})_3$, 2.4 mol % of ligand, 2 mL of TBME.

such as methyl (**2b**) and ethyl (**2c**), provided the desired product in moderate yields and moderate to excellent enantiomeric excess. Substituted olefins such as vinyl bromide **2d** and prenylated ketone **2e** were tolerated; however, only moderate enantiomeric excess was obtained. An ester (**2f**) and an α,β -unsaturated ethyl ester (**2g**) provided the desired products, again with only moderate selectivity. Alkyl substitution on the 2-position of the allyl was not well tolerated in the reaction, providing the product (**2h**) in low yield. Lastly, a variety of different benzyl derivatives performed well in the reaction, furnishing the corresponding alkylated products with good to excellent yields and excellent enantioselectivities (**2i**–**2l**).

With the scope established, we sought to examine our hypothesis pertaining to the formation of acyclic all-carbon quaternary stereocenters through reductive cleavage of the thioether (Scheme 2). When alkylation product **2a** was treated directly with Raney nickel in methanol at reflux, the desired desulfurization occurred; however, concomitant olefin hydrogenation was also observed. All attempts to prevent olefin

Scheme 2. Transformation of Alkylation Product to an Acyclic Ketone



hydrogenation while still achieving the desired desulfurization failed. To circumvent this issue, the allyl group can be functionalized prior to the desulfurization step, exemplified by the hydroboration–oxidation of **2a** prior to treatment with Raney nickel, providing acyclic ketone **3** with a synthetic handle for further manipulations.

In summary, we have developed an enantioselective Pd-catalyzed decarboxylative allylic alkylation of thiopyranones. Conditions were identified that tolerate the presence of the Lewis basic thioether, providing alkylated products in moderate to excellent levels of selectivity, with no issues of ring-opening β -elimination. While the cyclic products formed have multiple handles for further derivatization, the thioether can be reduced to afford desulfurized molecules containing an acyclic, all-carbon quaternary stereocenter. We envision that such acyclic α -quaternary ketones, as well as the parent thiopyranones, will find use in synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b02354](https://doi.org/10.1021/acs.orglett.7b02354).

Experimental procedures, characterization data, and vibrational circular dichroism determination of absolute stereochemistry (PDF)

NMR and IR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Selected reviews: (a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419–460. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5363–5367. (c) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593–4623. (d) Liu, Y.; Han, S. J.; Liu, W. B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740–751.
- (2) (a) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marunescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novak, Z.; Krout, M. R.;

McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. - Eur. J.* **2011**, *17*, 14199–14223. (b) Trost, B. M.; Xu, J.; Schmidt, T. J. *Am. Chem. Soc.* **2009**, *131*, 18343–18357.

(3) Batten, R. J.; Coyle, J. D.; Taylor, R. J. K.; Vassiliou, S. J. *Chem. Soc., Perkin Trans. 1* **1982**, 1177–1182.

(4) Jheengut, V.; Ward, D. E. *J. Org. Chem.* **2007**, *72*, 7805–7808.

(5) Hatano, M.; Ishihara, K. *Synthesis* **2010**, *2010*, 3785–3801.

(6) Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369–5372.

(7) Kang, J. Y.; Carter, R. G. *Org. Lett.* **2012**, *14*, 3178–3181.

(8) (a) Rovnyak, G. C.; Millonig, R. C.; Schwartz, J.; Shu, V. J. *Med. Chem.* **1982**, *25*, 1482–1488. (b) Shankaran, K.; Donnelly, K. L.; Shah, S. K.; Caldwell, C. G.; Chen, P.; Hagmann, W. K.; MacCoss, M.; Humes, J. L.; Pacholok, S. G.; Kelly, T. M.; Grant, S. K.; Wong, K. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5907–5911. (c) Tan, K.-L.; Ali, A.; Du, Y.; Fu, H.; Jin, H.-X.; Chin, T.-M.; Khan, M.; Go, M.-L. *J. Med. Chem.* **2014**, *57*, 5904–5918. (d) Cersosimo, U.; Sgorbissa, A.; Foti, C.; Drioli, S.; Angelica, R.; Tomasella, A.; Picco, R.; Semrau, M. S.; Storici, P.; Benedetti, F.; Berti, F.; Brancolini, C. *J. Med. Chem.* **2015**, *58*, 1691–1704. (e) Pan, J.; Xu, T.; Xu, F.; Zhang, Y.; Liu, Z.; Chen, W.; Fu, W.; Dai, Y.; Zhao, Y.; Feng, J.; Liang, G. *Eur. J. Med. Chem.* **2017**, *125*, 478–491. (f) Zhou, X.; Lin, K.; Ma, Z.; Chui, W.-K.; Zhou, W. *Eur. J. Med. Chem.* **2017**, *125*, 1279–1288.

(9) (a) Takemura, T.; Jones, J. B. *J. Org. Chem.* **1983**, *48*, 791–796. (b) Lane, S.; Quick, S. J.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 893–898. (c) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1397–1404. (d) Casy, G.; Sutherland, A. G.; Taylor, R. J. K.; Urban, P. G. *Synthesis* **1989**, 1989, 767–769.

(10) Ward, D. E.; Gai, Y.; Lai, Y. *Synlett* **1996**, 1996, 261–262.

(11) (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobé, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210–3213, 3215–3217.

(12) Ward, D. E. *Chem. Commun.* **2011**, *47*, 11375–11393.

(13) Sklute, G.; Marek, I. *J. Am. Chem. Soc.* **2006**, *128*, 4642–4649.

(14) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522–526.

(15) (a) Meyers, A. I.; Lefker, B. A. *Tetrahedron Lett.* **1987**, *28*, 1745–1748. (b) Moyers, A. I.; Westrum, L. J. *Tetrahedron Lett.* **1993**, *34*, 7701–7704. (c) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701–3705.

(16) Substrate synthesis required the use of a Dieckmann cyclization to form the cyclic β -ketoester, with other strategies such as α -acylation of the parent thiopyranone being unsuccessful. Additionally, attempts to prepare thiochromanone derivatives also failed.

(17) Bulkier alkyl groups were poorly tolerated in the reaction, providing low levels of enantioselectivity.