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Lewis acid mediated diastereoselective allylation of camphorpyrazolidinone derived α-ketoamides ☆

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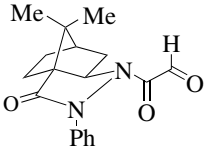
Abstract—Diastereoselective allylation of camphorpyrazolidinone derived α-ketoamides was examined using allyltributyltin in the presence of various Lewis acids. The corresponding optically enriched quarternary α-hydroxy carbonyls were obtained in reasonable to excellent material yields (51–95%) and with practical levels of stereoselectivity (up to >95% de) when a stoichiometric amount of $Sn(OTf)_2$ was used. The stereochemical induction is discussed.

Asymmetric carbonyl allylation represents one of the most useful tools for the construction of regio- and stereodefined carbon frameworks.[1] The alkene functionality is readily available for further functional group transformation.[2] The Lewis acid mediated allylation of aldehydes and imines derivatives to form chiral secondary homoallyl alcohols and amines is a highly useful synthetic operation and has been studied extensively.[3,4] The construction of chiral quarternary centers remains one of the most challenging frontiers in asymmetric synthesis.[5] Diastereoselective allylation of chiral α-keto carbonyls bearing a chiral auxiliary using allylic silanes and stannanes have been reported.[6] We wish to report here on the diastereoselective addition of allyltributyltin reagent to various camphorpyrazolidinone derived α-ketoamides **2**. Good to excellent diastereoselectivies (up to >95% de), with high material yields were realized when **2** was used.



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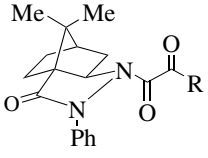

2a: R = Ph
2b: R = Me
2c: R = Et
2d: R = 2-thiophene

The starting camphorpyrazolidinone **1** was designed and synthesized in this laboratory and has proven to be an efficient chiral auxiliary in asymmetric synthesis.[7] The starting chiral α-ketoamides (**2**) were readily prepared by the condensation of camphorpyrazolidinone **1** with the corresponding α-keto acid chlorides under standard conditions. Camphorpyrazolidinone phenylglyoxylate (**2a**) was chosen for use as a model compound and various conditions were examined. No desired product was observed when **2a** was treated with allyltributyltin in the absence of a Lewis acid. The use of $Eu(OTf)_3$ (1.0 equiv) provided the desired product in 50% material yield when the reaction was carried out in CH_3CN as the solvent (Table 1, entry 1). The chemical yield was significantly improved to 93% yield when $Zn(OTf)_2$ was used in 40 min (entry 2). To our surprise, a high stereoselectivity was achieved (92% de) as indicated by ^1H NMR analysis of the relevant peak from the crude products. The absolute stereochemistry of the newly generated stereogenic center was assigned as an *R* configuration by single crystal X-ray analyses of **3a**. A careful inspection of ^1H NMR spectra indicates that the characteristic C2 methine proton (camphor numbering) appears at 3.4 ppm (usually at 4.0 ppm for similar derivatives). The diamagnetic anisotropy effect of the benzene ring may account for the shielding effect. Comparable stereoselectivity was obtained when **2a** was

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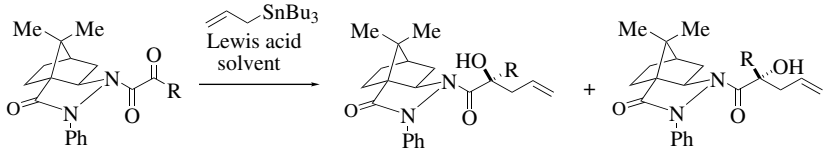
Table 1. Diastereoselective allylation of camphorpyrazolidinone derived α-ketoamides (**2**) with allyltributyltin[a]



2a-d **3** **4**

Entry		Solvent	Lewis acid (equiv)	*t*/h	Yield (%)[b]	Dr (**3**:**4**)[c]
1	**2a**	CH_3CN	$Eu(OTf)_3$ (1.0)	72	50	72:28
2	**2a**	CH_3CN	$Zn(OTf)_2$ (1.0)	2/3	93	96[d]:4
3	**2a**	CH_3CN	$Sn(OTf)_2$ (1.0)	1/12	95	99:1
4	**2a**	THF	$Sn(OTf)_2$ (1.0)	1/12	91	99:1
5	**2a**	CH_2Cl_2	$Sn(OTf)_2$ (1.0)	48	<10	nd[e]
6	**2a**	Toluene	$Sn(OTf)_2$ (1.0)	48	<10	nd
7	**2a**	CH_3CN	$Sn(OTf)_2$ (0.5)	1/6	85	99:1
8	**2a**	CH_3CN	$Sn(OTf)_2$ (0.1)	10	26	99:1
9	**2b**	CH_3CN	$Sn(OTf)_2$ (1.0)	1/12	89	77:23
10	**2b**[f]	CH_3CN	$Sn(OTf)_2$ (1.0)	1	91	79:21
11	**2b**	CH_3CN	$Zn(OTf)_2$ (1.0)	3	90	88:12
12	**2b**[f]	CH_3CN	$Zn(OTf)_2$ (1.0)	20	87	90:10
13	**2b**[g]	CH_3CN	$Zn(OTf)_2$ (1.0)	48	85	89:11
14	**2b**	CH_3CN	$Eu(OTf)_3$ (1.0)	72	51	26:74[d]
15	**2c**	CH_3CN	$Sn(OTf)_2$ (1.0)	1/12	91	83:17
16	**2d**	CH_3CN	$Sn(OTf)_2$ (1.0)	1/12	92	99:1

[a] Unless specifically noted, all reactions were carried out using **2** (0.15 mmol), allyltributyltin (2.0 equiv), Lewis acid and solvent as indicated at ambient temperature.
[b] Total isolated yield (**3**+**4**).
[c] Determined by ^1H NMR analysis of the relevant peaks and/or HPLC analysis [(Daicel chiracel chiral OD column: 2-propanol/hexane = 5:95 (1.0 mL/min))] from the crude products.
[d] The absolute stereochemistry of the newly generated stereogenic center was determined to have an *R* configuration by single crystal X-ray analyses of **3a** and **4b**.
[e] Not determined.
[f] Reaction carried out at 0 °C.
[g] Reaction carried out at −30 °C.

treated with allyltributyltin in the presence of $Sn(OTf)_2$ in 5 min (entry 3). The effect of solvent was then studied under the same reaction conditions and the results indicated that CH_3CN and THF were the two most suitable solvents for the allylation addition (entries 4–6). The effect of the molar ratio of the Lewis acid to the substrate was next studied. Although the stereoselectivity remained unchanged, the reactivity decreased when less than an equivalent amount of Lewis acid was used (entries 7 and 8). For example, the use of 0.1 equiv of $Sn(OTf)_2$ gave the desired product in only 26% yield after 10 h under the same reaction conditions. The levels of facial selectivity obtained are comparable with the highest levels of diastereoselectivity reported in the allylation of chiral α-dicarbonyls.

To test the feasibility of the allylation addition various α-ketoamides **2b–d** were examined in the reaction. The use of camphorpyrazolidinone pyruvate **2b** gave the desired product in moderate stereoselectivity and the reactivity decreased when the reaction was carried out at 0 °C (entries 9 and 10). Slight improvement in stereoselectivity and a decrease in reactivity were observed when $Zn(OTf)_2$ was used. The allylation of **2b** is insensitive to reaction temperature (entries 11–13). Interestingly, the stereoselectivity was reversed when $Eu(OTf)_3$ was used (entry 14). This may be due to the different mode of coordination of the metal atom to the carbonyl oxygen atoms. Comparable results were obtained when *N*-ketobutyrate **2c** was used in the presence of $Sn(OTf)_2$ (entry 15). Excellent selectivity was obtained when 2-thiophene substituent **2d** was used (entry 16).

The stereochemical bias of the present study can be rationalized by the conformational preference of α-ketoamides **2** in the transition state.[5b] The pseudo planar *s-trans* conformation (A) of the α-dicarbonyl group in **2** is electronically favored over its *s-cis* conformer (A′) in the solid state and this is supported by the single crystal X-ray analyses of **2a** and **2b** (Fig. 1). This is due to the avoidance of dipole repulsion of the two carbonyl functionalities. However, in the presence of a Lewis acid, the coordination of the metal ion to the dicarbonyl

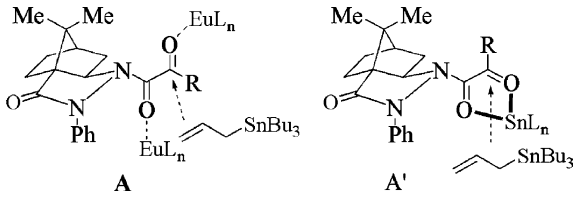


Figure 1. Proposed mechanism for the reaction of α-ketoamides **2** with allyltributyltin in the presence of Lewis acid.

oxygen atoms resulted in the formation of the preferred *s-cis* conformation. The equilibrium of different conformational states are highly dependent upon the type and amount of Lewis acid used in the reaction. For Lewis acids such as $Eu(OTf)_3$, monocoordination of the metal to carbonyl oxygen atom in **2b** is favored and the *s-trans*-like conformation dominates. The allylic reagent then approaches from the less hindered bottom *re* face to give the desired major isomer (entry 14). On the other hand, both Lewis acids [$Sn(OTf)_2$ and $Zn(OTf)_2$] coordinate to dicarbonyl oxygen atoms, resulting in a conformational equilibrium shift toward the *s-cis* arrangement (A′). The major diastereoisomer is obtained when the allyl reagent attacks the α-carbonyl group from the less hindered bottom *si* face, to afford the desired product.

In summary, the diastereoselective allylation of various camphorpyrazolidinone derived α-ketoamides (**2**) with allyltributyltin was examined. The corresponding optically enriched quarternary α-hydroxy carbonyls were obtained in reasonable to excellent material yields (51–95%) and in good to excellent stereoselectivity when $Sn(OTf)_2$ was used (up to >95% de). The *s-cis* conformation of the α-dicarbonyl functionality is highly favored in the transition state when strong Lewis acids such as $Zn(OTf)_2$ and $Sn(OTf)_2$ are used. The allyl reagent attacks from the less hindered bottom *si* face to give the desired product. Further studies of the allylation of camphorpyrazolidinone derived *N*-glyoxylate and its derivatives are currently underway.

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References and notes

1. For reviews, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10, pp 299–402; (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11, pp 403–490; (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 207.
2. (a) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495; (b) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953.
3. For recent allylation reaction, see: (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160; (b) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414; (c) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488, and references cited therein; For diastereoselective allylation of chiral aldehydes, see: (d) Kiegiel, K.; Prokopowicz, P.; Jurczak, J. *Synth. Commun.* **1999**, *29*, 3999; (e) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833; (f) Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.
4. Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454.
5. (a) Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970; (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591; (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.
6. (a) Raszphewicz, K.; Sikorska, L.; Kiegiel, K.; Jurzcak, J. *Pol. J. Chem.* **2002**, *76*, 1595; (b) Kiegiel, K.; Jurczak, J. *Tetrahedron Lett.* **1999**, *40*, 1009; (c) Kim, Y. H.; Kim, S. H. *Tetrahedron Lett.* **1995**, *36*, 6895; (d) Kawanami, Y.; Katayama, K. *Chem. Lett.* **1990**, 1749; (e) Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290; (f) Boireau, G.; Korenova, A.; Deberly, A.; Abenhaim, D. *Tetrahedron Lett.* **1985**, *26*, 4181; (g) Ojima, I.; Miyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976**, 927; For other allylation of α-dicarbonyl groups, see: (h) Shin, J. A.; Cha, J. H.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kang, H.-Y.; Cho, Y. S. *Tetrahedron Lett.* **2001**, *42*, 5489; (i) Nair, V.; Jayan, C. N.; Ros, S. *Tetrahedron Lett.* **2001**, *57*, 9453; (j) Fukuzawa, S.-i.; Miura, M.; Matsuzawa, H. *Tetrahedron Lett.* **2001**, *42*, 4167; (k) Gewald, T.; Kira, M.; Sakurai, H. *Synthesis* **1996**, 111; (l) Takuwa, A.; Nishigaichi, Y.; Yamashita, K.; Iwamoto, H. *Chem. Lett.* **1990**, 1761.
7. (a) Fang, C. L.; Lee, W.-D.; Teng, N. W.; Sun, Y.-C.; Chen, K. *J. Org. Chem.* **2003**, *68*, 9816; (b) Fang, C. L.; Lee, W.-D.; Reddy, G. S.; Chen, K. *J. Chin. Chem. Soc.* **2003**, *50*, 1047; (c) Yang, K. S.; Chen, K. *J. Org. Chem.* **2001**, *66*, 1676; (d) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729; (e) Yang, K. S.; Lain, J. C.; Lin, C. H.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 1453; (f) Lin, C. H.; Yang, K. S.; Pan, J. F.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 6815.